Longitudinal Evaluation of Training-Induced Neural Plasticity

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Contents

Summary

Neuroplasticity is reflected in the great capacity of the human brain to adapt quickly and efficiently to a broad variety of environmental factors, and comprises an essential prerequisite for learning. In line with the idea of a plastic human brain, previous neuroimaging studies in the field of motor learning have shown that learning a new skill evokes substantial neuroanatomical and neurofunctional changes. Moreover, there is strong evidence that these motor skill training-induced neuronal adaptations occur across the entire lifespan, from birth to old age. However, the neuronal underpinnings of training-induced adaptations in subjects in the middle adulthood have received little scientific attention. Furthermore, previous studies investigating training-induced neuroplasticity focussed rather on strict training protocols than on physical activities practiced as a leisure activity.

By aligning a longitudinal study design with two measurement time-points, the present dissertation thesis aims to explore the dynamic processes of brain anatomy and brain function induced by a highly complex motor training practiced as leisure activity in participants between the age of 40 to 60 years. The investigated motor learning task consisted of golf training practiced as leisure activity. Learning to play golf puts high demands on motor and cognitive abilities and is a physical leisure activity that is not restricted to a certain age group. The first study focussed on anatomical changes induced by the motor-training, whereas the second study focussed on changes of functional neuronal recruitment patterns while mentally performing a golf swing.

In order to investigate the neuroanatomical underpinnings of training-induced neuroplasticity in golf novices, the first study used structural magnetic resonance imaging (MRI) and the method of voxel-based morphometry. As a main result, the 40 hours of golf practice, performed as a leisure physical activity with highly individual training protocols, have shown to be associated with gray matter increases in a task-relevant cortical network. These substantial neuroanatomical changes were revealed in regions of the sensorimotor cortex and areas belonging to the dorsal stream. It is suggested that these brain regions play a crucial role during the process of motor learning and the control of visuomotor coordination. The control subjects did not show any gray matter changes in these or in other brain areas. Interestingly, those golf novices who practiced most intensively within the 40-hour period demonstrated the strongest neuroanatomical changes in a critical region of the dorsal information stream. These findings demonstrate that a physical leisure activity induces training-dependent changes in gray matter and let assume that a strict and controlled training protocol is not necessary for training-induced adaptations of gray matter.

The second study aimed to investigate changes of neuro-functional recruitment patterns

that can be ascribed to the golf training, by using the method of functional MRI (fMRI) and a motor imagery task. The analyses revealed increased hemodynamic responses during the mental rehearsal of a golf swing in non-primary cortical motor areas, subcortical motor areas and parietal regions in the novice golfers and the control subjects. This result complements previous mental imagery research showing the involvement of motor areas while mentally rehearsing a complex movement, especially in subjects with low skill level. More importantly, only the golf novice group showed changes between the two measurement time-points. Hemodynamic responses were decreased in non-primary motor areas after the 40 hours golf practice interval. Thus, the results indicate that in the barely studied population of middle-aged adults, a complex physical leisure activity induces functional neuroplasticity. This finding supports the idea that an improvement of skill level is associated with a more efficiently working neuronal network.

Zusammenfassung

Eine grundlegende Voraussetzung für das Lernen ist die neuronale Plastizität, welche sich durch eine schnelle und effiziente Anpassungsfähigkeit des Gehirns an eine Vielzahl von Umweltfaktoren widerspiegelt. Anhand bildgebender Studien auf dem Gebiet der Neuroplastizität und im Bereich des motorischen Lernens konnte gezeigt werden, dass das Erlernen einer neuen Bewegung erhebliche Veränderungen sowohl auf neuroanatomischer als auch auf neurofunktioneller Ebene hervorruft. Des Weiteren zeigen neuere Forschungsergebnisse, dass das Gehirn diese Kapazität zur Anpassung bis ins hohe Alter beibehält. Bis zum heutigen Zeitpunkt liegen kaum Befunde vor, die die Formbarkeit des Gehirns im mittleren Erwachsenenalter untersucht haben. Zudem sind in früheren Längsschnittsstudien auf dem Gebiet der trainings-induzierten neuronalen Plastizität vorwiegend strikte Trainingsprotokolle angewandt worden und die Frage, ob eine Freizeitaktivität ähnliche neuronale Veränderungen hervorruft, blieb bis anhin unbeantwortet.

Die vorliegende Arbeit hat zum Ziel, mittels eines Längsschnittsstudiendesigns mit zwei Messzeitpunkten den Einfluss eines anspruchsvollen 40-stündigen motorischen Trainings auf die Gehirnanatomie und die Gehirnfunktion zu untersuchen. Die Probanden waren Golfanfängerinnen- und anfänger im mittleren Alter, die Golf als Freizeitaktivität trainierten. Für das Erlernen des Golfspiels sind hohe kognitive und motorische Fähigkeiten erforderlich. Zudem kann das Erlernen dieser Sportart nicht einer bestimmten Altersgruppe zugeordnet werden, weshalb sie auch bei vielen Leuten im mittleren Alter hohen Anklang findet. In der ersten Studie wurden trainings-induzierte Veränderungen in der Neuroanatomie erforscht, während die zweite Studie funktionelle Veränderungen beim mentalen Vorstellen eines Golfschwungs untersuchte.

Mithilfe der strukturellen Magnetresonanztomographie wurden in der ersten Studie zu beiden Zeitpunkten neuroanatomische Parameter gemessen. Dadurch konnten intra individuelle Veränderungen der grauen Substanz erforscht werden, welche durch das motorische Golftraining induziert wurden. Die Datenanalyse wurde anhand der voxelbasierten Morphometrie durchgeführt. Die Ergebnisse dieser Studie zeigen, dass ein 40-stündiges Golftraining bei Probanden im mittleren Erwachsenenalter deutliche strukturelle Veränderungen hervorruft. Die Kontrollgruppe, die keine neue Fertigkeit geübt hat, zeigt dagegen keine neuroanatomischen Veränderungen zwischen den beiden Messzeitpunkten. Insbesondere in Gehirnarealen, die sowohl beim Erlernen von motorischen Fertigkeiten als auch bei der visuomotorischen Verarbeitung eine wichtige Funktion übernehmen, nahm das Volumen der grauen Substanz als Folge des Trainings zu. Ein interessanter Befund ist, dass die Veränderungen in einem für die visuomotorische Verarbeitung wichtigen Areal stark von der Trainingsintensität abhängig sind. Diese Ergeb-

nisse zeigen, dass eine Freizeitaktivität substanzielle Veränderungen in der grauen Substanz auslösen kann und es dazu kein striktes Trainingsprotokoll braucht.
Die zweite Studie hatte zum Ziel, Veränderungen im Aktivierungsmuster während dem Ausführen eines mentalen Golfschwungs zu untersuchen. Diese Studie wurde mit Hilfe der funktionellen Magnetresonanztomographie durchgeführt. Während dem mentalen Vorstellen des Golfschwungs zeigten sich bei den Golfanfängern und bei den Kontrollversuchspersonen erhöhte hämodynamische Antworten sowohl in sekundär motorischen als auch in sub-kortikal motorischen Regionen und im Parietallappen. Dieser Befund bestätigt die Resultate früherer Studien, die darauf hingewiesen haben, dass ein grosses sensomotorisches Netzwerk aktiviert wird, wenn eine Bewegung mental vorgestellt wird - dies insbesondere bei Anfängern. Allerdings zeigte nur die Golfgruppe Unterschiede in der neuronalen Rekrutierung zwischen den beiden Messzeitpunkten. Dies widerspiegelte sich in einer Abnahme der neuronalen Aktivierung im prämotorischen Kortex. Die Ergebnisse der zweiten Studie zeigen, dass das Erlernen einer komplexen Sportart wie Golf funktionelle Neuroplastizität induziert und unterstützen somit die Hypothese, dass eine Zunahme der Fertigkeit mit einem effizienter arbeitenden neuronalen Netzwerk einhergeht.

1 Introduction

> *"Our challenge is to modulate neural plasticity for optimal behavioral gain, which is possible, for example, through behavioral modification and through invasive and non-invasive cortical stimulation."*
> (Pascual-Leone et al., 2005, p. 396)

By:

1. the intervention of a physical activity,
2. the application of a longitudinal study design,
3. the methods of structural and functional magnetic resonance imaging,

   and

4. the investigation of participants in the middle adulthood, ...

... the present work accepts this challenge!

Learning a new motor action requires a good functioning network that includes the musculoskeletal system as well as the peripheral and central nervous system. From an ontogenetic perspective skill learning is one of the core processes of human development. This is particularly true during the early stages of development where elementary motor actions need to be learned. Aside from learning elementary movements, the acquisition of a new physical activity is considered as a less age-restricted kind of motor skill learning.
Motor learning - of either a simple elementary movement or a complex physical activity - is reflected on behavioral and on neuronal level by its dynamic characteristics. The present work intends to shed more light onto these dynamic processes by using a longitudinal study design. Data derived from a longitudinal design are needed in order to describe the full individual potential of structural and functional adaptation of the nervous system in the context of skill learning, in particular in early learning stages.
Irrespective of the kind of skill learning, the brain needs to adapt fast and efficiently as a response of motor learning processes in order to meet the new requirements. Consequently, the brain's adaptivity might be reflected in a changed anatomical architecture

or a changed functional recruitment pattern. Recent research has pointed out that the brain's capability to learn a new and complex movement is not limited to children but rather comprises the whole lifespan. Thus, independent of age, learning a new physical activity has shown to induce neuroanatomical and neurofunctional changes, which is also termed as structural and functional plasticity.

Evidence for the capacity of neuroplasticity occurring throughout the whole lifespan bases mainly on the comparison between a young (i.e., between 20 and 30 years) and an old (i.e, older than 65) study population. Although age comparison studies are rare, it is suggested that age has a potential influence onto the extent and pattern of neuroplastic adaptations. However, the age-cohort between the age of 40 and 60 years has been largely neglected by neurophysiological research for a long time and mechanisms of neural plasticity as a consequence of motor learning in that specific age period are insufficiently understood.

Summarily, the present work tries to extend our knowledge about motor learning induced plastic adaptations of the human brain.

2 Theoretical background

2.1 Neuroplasticity

The human brain demonstrates an enormous capacity to adapt and modify – quickly and efficiently – to a broad variety of environmental demands, physiologic changes, chemicals, and experiences. This intrinsic property of the nervous system is termed "neuroplasticity" (Jäncke, 2009; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Nowadays, the theoretical framework of neuroplasticity is attracting a great deal of attention from a broad field of research - ranging from animal research, molecular research and clinical research to psychological research, just to name a few. Despite of its great impact on the present scientific work, lifespan neuroplasticity, which refers to the changes of structure and function across all age groups, has long been neglected by the neuroscientific community. One of the pioneers in the neuroplasticity research was Donald O. Hebb (Jäncke, 2009), who proposed the Hebbian learning theory in 1949. The following quote from Donald O. Hebb is still regarded as a possible explanation for the neuronal underpinnings of learning:

> "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased (Hebb, 1949, p. 62)."

However, this view of a highly adapting, i.e., plastic human brain has not regained attention until the late 80's of the last century. It is important to note, that as early as in the 1970's, animal research already provided promising indications for changed cortical patterns as a consequence of altered experience. Two possible explanations might be considered for the late neuroplasticity "revival". First, neuroplasticity has been regarded as a strong correlate of learning, which has long been considered as a process that is restricted to a certain age phase, namely the age period from early childhood to young adulthood. Therefore, neuroplasticity was considered a process that occurs only during a critical age period. This overestimated relationship of learning and age may be regarded as a possible reason for the neglected potentials of neuroplasticity. Second, the modern neuroimaging methods, such as the magnetic resonance imaging methods, provided a breakthrough for the non-invasive investigation of the healthy human brain. By means of this method and a revised assumption on the neuronal underpinnings of learning, research on structural and functional neuroplasticity of the last 20 years has provided numerous interesting findings. These findings provide strong evidence that neuroplasticity occurs across the entire lifespan – from birth to old age (Lustig, Shah,

Seidler, & Reuter-Lorenz, 2009; Seidler, 2007).
This new perception of neuroplasticity provided an interesting docking site for basic research as wells as for research taking a more clinical perspective. For example the mechanisms of focal hand dystonia in musicians could be explained by the concept of neuroplasticity by demonstrating the pathological consequence of neuroplasticity (Chamagne, 2003). It is thought that the cortical reorganization processes in focal hand dystonia are the consequence of a too excessive instrumental practice. On the other hand, neuroplasticity may also be considered as an opportunity to provide an intervention approach during neurorehabilitation (Pascual-Leone et al., 2005). Transient functional neuroplasticity may be induced for example by applying transcranial magnetic stimulation (TMS) on a specific cortical region. Thus, a changed neuronal recruitment pattern (i.e., functional neuroplasticity) may compensate for a lesioned brain area or a pathological neuronal network.

2.1.1 Structural and functional neuroplasticity

The consequence of neuroplasticity may be either manifested by morphologic changes or functional changes. In respect of the investigated focus, i.e., morphologic or functional changes, "neuroplasticity" might be termed as (a) structural or (b) functional neuroplasticity. Although, this classification is frequently used in the present literature (also in the present dissertation) it is important to note that structural and functional neuroplasticity can not be dichotomized and thus a clear segregations is not possible. Functional and structural neuroplasticity may rather be regarded as two processes with a mutual interaction. This means, that morphologic changes are accompanied by functional changes and vice-versa. With respect to the different methodological approaches to study neuroplasticity, there is a practical differentiation based on the spatial and temporal methodological characteristics. Structural neuroplasticity is mainly investigated by means of structural magnetic resonance imaging (MRI), whereas studies focussing on functional neuroplasticity are using methods such as electroencephalography (EEG), TMS, or functional magnetic resonance imaging (fMRI).
The research line of structural neuroplasticity focuses predominantly on the morphologic changes, i.e., anatomical changes due to experiences or learning, mainly by using T1-weighted MR-images with a high resolution. In general, these studies showed macroanatomical changes in gray and white matter that can be ascribed to experiences or learning. A well-known study in the research field of structural neuroplasticity is the study by Amunts and colleagues (1997) demonstrating that the cortical hand motor region of professional piano players is enlarged compared to non-musicians. It was suggested that this anatomical change in the hand motor region is the consequence of the long-lasting and intense piano practice (Amunts et al., 1997).
So far, there is still limited knowledge regarding the cellular mechanisms of structural neuroplasticity (Draganski et al., 2006; van Praag, Kempermann, & Gage, 1999). Animal research provides an advisable method to study the underlying cellular mechanisms of the macroscopic changes. It is speculated that morphologic changes in cortical brain

areas may be the result of changes in the dendritic spine volume (Holtmaat & Svoboda, 2009) or of experience-dependent synaptogenesis (Trachtenberg et al., 2002). This means that a new experience might give rise to synaptogenesis, that is reflected in an increased amount of synapses and consequently in a more densely packed cortex. Besides synaptogenesis, neurogenesis has also been regarded as potential cellular mechanism for the experience-dependent macroscopic changes. However, this cellular process has shown to be restricted to the hippocampal region only and not to the entire cortex (Eriksson et al., 1998; Kempermann & Gage, 1998).

Considering functional neuroplasticity, pioneer work with adult monkeys demonstrated that the cortical representation of the somatosensory map changes as a consequence of a drastic sensory experience, namely the amputation of the monkey's finger (Merzenich et al., 1984). Following this procedure, the cortical representation in the somatosensory cortex of the neighbored fingers changed and expanded into the territory of the amputee finger. Approximately 10 years later, further evidence for functional plasticity came from human research using non-invasive neuroimaging methods, i.e., fMRI, EEG and TMS. These studies demonstrated that neurophysiological activation patterns change as a consequence of learning or experiences (*for reviews see:* Jäncke, 2009; Pascual-Leone et al., 2005).

Depending on the utilized method, the underlying mechanisms of changed neurophysiological activation patterns refer either to (a) changed hemodynamic responses (fMRI), (b) changed electrical potentials (EEG), or (c) changed motor evoked potentials (TMS). It is suggested that these spatial and/or temporal changes in neuronal recruitment base upon pre-existing, albeit unincisive, connections between related brain regions (Pascual-Leone et al., 2005). Hence, this compensation process might be predicated by an unmasking of pre-existent pathways.

2.1.2 Cross-sectional expert studies

Neuroplasticity is strongly associated with learning and experience. The investigation of structural and functional neuroplasticity can be studied by two kinds of experimental designs - (a) cross-sectional expert studies or longitudinal novice studies. This section (2.1.2) focusses on cross-sectional study designs with motor-experts, whereas the next section (2.1.3) refers to studies investigating motor-learning by means of longitudinal study designs.

Expertise is the result of an intensive involvement with a certain task and long-lasting training sessions. For example, professional musicians are characterized by the early onset of an intense and often life-long musical practice, and therefore constitute an ideal study sample to investigate structural and functional neuroplasticity (Münte, Altenmüller, & Jäncke, 2002). In order to perform a musical instrument at the highest stage, very complex motor and sensory abilities are needed. An elegant way to investigate neuroanatomical and neurophysiological correlates of the expertise and its associated trained abilities is facilitated by comparing an expert group with an non-expert group. In the case of professional musicians, expertise is expected in the sensorimotor

and auditory domain. In other words, group-differences may indicate where (anatomically) and how (functionally) neuroplasticity occur throughout the process of learning or training respectively. The next two sections present studies predominantly investigating neuroplasticity in the sensorimotor system, given the focus of this dissertation. One partition focuses on structural neuroplasticity and the other focuses on functional neuroplasticity.

Structural neuroplasticity

With the emergence of the new imaging methods studies have begun to provide evidence for anatomical peculiarities of the musician's brain and, thus, for structural neuroplasticity (*for reviews see:* Jäncke, 2009; Münte et al., 2002). Amongst others, these anatomical characteristics of professional musicians included an enlarged hand motor area (Amunts et al., 1997), a larger corpus callosum size (Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995), increased gray matter values in motor- and auditory relevant areas (Gaser & Schlaug, 2003), and a changed white matter architecture in the corticospinal tract (Imfeld, Oechslin, Meyer, Loenneker, & Jäncke, 2009). Taken together, these studies demonstrate that changes in gray and white matter architecture are the consequence of the highly complex motor and auditory training in musicians.
Besides professional musicians, highly trained athletes have been found to be a good alternative population for studying long-term plasticity. However, considering structural neuroplasticity, only a few studies have been conducted, so far. Along these lines, it has been shown that the gray- and white-matter architecture of professional golf players differs from the morphology of less skilled golf players (Jäncke, Koeneke, Hoppe, Rominger, & Hanggi, 2009). In task relevant cortical regions (i.e., the fronto-parietal network), the professional golf players revealed increased gray-matter values compared to the less skilled golf group. Another study conducted by the same research group, reported similarly training-induced anatomical differences in the sensorimotor system of professional ballet dancers compared to a control group (Hanggi, Koeneke, Bezzola, & Jäncke, 2010). These findings by the group of Jäncke were partially confirmed by another group investigating the anatomical peculiarities of professional basketball players, which showed training-induced effects in sub-cortical structures, namely the basal ganglia (I. S. Park et al., 2011) and in the cerebellum (I. S. Park et al., 2009). It has to be mentioned, that no group differences were existent when analyzing the entire cerebellum (in terms of one volume) (I. S. Park et al., 2006). Taken together, these findings provide support for the idea that gray- and white matter in task-relevant anatomical regions are prone to training-induced structural plasticity.
However, other factors than training have been shown to play a crucial role onto the underlying mechanisms of structural neuroplasticity. In these studies, which focussed on broad variety of experiences, covariates, such as age and lifestyle factors (e.g., physical fitness), were correlated with anatomical measures instead of expertise. Although research of the last decade provides strong evidence that these training-induced changes occur across the entire lifespan – from birth to old age (Lustig et al., 2009; Seidler, 2007),

there is also evidence that age has an influential effect onto the process of plasticity. In other words, the extent of training-induced neuronal adaptations showed to decline with increasing age (Boyke, Driemeyer, Gaser, Buchel, & May, 2008). Besides the influence of age on structural neuroplasticity, a healthy and active lifestyle has shown to affect brain plasticity positively and this factor has been suggested to counteract (or influence) age-related losses (Gordon et al., 2008; Rovio et al., 2010; Verghese et al., 2003). Even if these studies suggest potential factors of experience-dependent neuroplasticity, methodological flaws have to be taken into account, in particular when considering the influence of lifestyle factors, such as leisure activities, physical fitness and education. A cross-sectional study design has the disadvantage that these data need to be collected retrospectively by means of questionnaires. Thus, the brain-behavior correlation is only indirectly measured and the impact of other unspecific covariates cannot be excluded.

Functional neuroplasticity

In contrast to the previous subsection, studies investigating functional neuroplasticity are characterized by the application of methods with the focus on temporal and spatial characteristics, such as fMRI, EEG and TMS. In regarding similarities between the two types of neuroplasticity, professional musicians and athletes have shown to be an ideal study population for studying the functional correlates of expertise. Professional musicians demonstrated a distinct cortical activation pattern when performing music-related hand movements, because this motor task shows similarities to their expertise (e.g., playing the piano) (Jäncke, Shah, & Peters, 2000; Koeneke, Lutz, Wustenberg, & Jäncke, 2004; Hund-Georgiadis & von Cramon, 1999; Krings et al., 2000; Lotze, Scheler, Tan, Braun, & Birbaumer, 2003). In contrast to non-musicians, professional musicians recruited a reduced neuronal network during the performance of uni- and bi-manual movements. This decrease of neuronal recruitment was particularly dominant in motor regions, including the primary motor cortex and secondary motor areas (premotor cortex PMC, supplementary motor area SMA). These findings let assume that motor experts might execute or prepare a motor task more efficient, with less effort, and with fewer degrees of freedom (Bernstein, 1967; Jäncke et al., 2000). The latter refers to a theoretical view, which suggests that a higher skill level is accompanied by a more conjointly motor control. Through experience this control process makes use of synergies by functionally linking together different effectors (e.g., number of limbs, joints, etc.) - meaning that more effectors may be supervised simultaneously, without the need to control each effector separately (Tuller, Turvey, & Fitch, 1982).
Although the training intensity for professional athletes might be lower compared to professional musicians, effects of functional plasticity have consistently been reported (Calvo-Merino, Glaser, Grezes, Passingham, & Haggard, 2005; Milton, Solodkin, Hlustik, & Small, 2007; Olsson, Jonsson, Larsson, & Nyberg, 2008; Wei & Luo, 2010). In general, professional athletes have also been shown to recruit a smaller neuronal network while performing an expertise-relevant task. In contrast to playing a musical instrument, performing a physical activity (e.g., dancing, playing golf, etc.) relies often on complex

movements including several joints and muscles or even different body parts. Instead of the execution of real movements, one has thus to rely on an alternative task that can be applied despite the spatial constraints of the MR-tomograph. This alternative bases upon the close neuronal relationship of imagined and executed movements and is termed "motor imagery" (see 2.2.5). By using this approach, Milton and coauthors demonstrated that the organization of the involved neuronal network during the pre-shot routine of a golf swing differs in respect to expertise (Milton et al., 2007). In contrast to golf novices, golf professionals recruited a more focused and less spatially distributed neuronal network during the preparatory phase that precedes the golf swing. Similarly, Olsson and coauthors support this finding by showing that professional high-jumpers recruit a distinct neuronal pattern for the mental rehearsal of high-jump movements, whereas the novices rely on a distributed and less specific neuronal network (Olsson, Jonsson, Larsson, & Nyberg, 2008). This findings corroborate well to the previous described research line, i.e., training-induced functional neuroplasticity in professional musicians, and leads to the assumption that professionals need less cognitive control to control for automized movement patterns.
In line with research investigating structural neuroplasticity, it was shown that expertise is not the only factor influencing the underlying mechanisms of training-induced functional plasticity. The effect of age showed similarities to the effect of expertise, meaning that older subjects, compared to younger subjects, rely on a larger neuronal network in order to perform the same sensorimotor task (Heuninckx, Wenderoth, & Swinnen, 2008). This finding is consistent with the compensation hypothesis (D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Lustig, 2005) suggesting that with increased age, the brain recruits additional neuronal networks in order to compensate for various age-related neural and behavioral losses.

2.1.3 Learning-induced plasticity

The breakthrough of training-induced structural and functional neuroplasticity was achieved by means of cross-sectional study designs, but this type of design is also associated with disadvantages. Cross-sectional study designs may only be indicated when longterm-training, experience, or only the far most end of the learning process is focused. As a result a longitudinal study design is more adequate in order to investigate early learning stages or the short-term effects of training-induced neuroplasticity. This type of design enables to track individual changes, since for each participant data from different time-points are collected. Hence, the criteria for the study sample is not restricted to professionals (as in the previous described cross-sectional designs), but the investigation of novices that learn a new motor task is feasible - meaning that also very early stages of learning are examinable. Besides the advantage of the learning stage and the expertise-independency, a longitudinal study design may also shed more light on the temporal properties of neuroplasticity. This allows for a more dynamic perspective to be chosen (Draganski & May, 2008). This section focuses on longitudinal studies investigating the early learning stages of interventions, in particular motor trainings, and its associated

structural and functional neuronal correlates.

Structural neuroplasticity

Longitudinal studies investigating training-induced changes in anatomical properties of the cortical motor system are generally rare. One of the first studies of this type was the study from Draganski and coauthors (Draganski et al., 2004) that demonstrated the impact of a visuo-motor training on the gray matter properties. In that study, an experimental group (with no pre-experience in juggling), which learned to juggle for a duration of three months, was compared to a passive control group. In order to track changes over time, the authors aligned a longitudinal study design with three structural MR-measurement time-points. Besides a pre- and post-collection (i.e., after three months) of structural brain images, three months after the second scan an additional third measurement was carried out. Between the second and third scan, none of the participants (neither experimental nor control group participants) performed the visuo-motor training. This study revealed two main findings. First, only the juggling group demonstrated changes in gray matter after three months of juggling (i.e. between scan 1 and scan 2). The increases of gray matter were located in extrastriate visual cortex and the parietal lobe. These two areas play a pivotal role in the visual perception of movement and also in the visuo-motor transformation, which in this connection are most likely associated with the juggling training. The second main finding confirmed the assumption that these changes in gray matter are associated with the juggling training. Accordingly, when participants ceased the training the gray matter volumes reversed towards the baseline level. Taken together, this study was the first to demonstrating training-related structural changes in untrained subjects (Draganski et al., 2004). Several follow-up studies were performed in order to shed more light on the issue of training-induced anatomical changes. The main findings of these studies are the following: (a) training induced changes already emerge after the first training week (Driemeyer, Boyke, Gaser, Buchel, & May, 2008), (b) participants aged 65 and older demonstrated similar, however, not identical structural changes of gray matter compared with the younger study sample (Boyke et al., 2008), and (c) the juggling training induced changes not only in gray matter but also in white matter properties as measured by diffusion tensor imaging (DTI) (Scholz, Klein, Behrens, & Johansen-Berg, 2009).

Not only juggling but also other types of motor training were shown to influence brain structure. In a recent neuroimaging study, the authors demonstrated that two single training sessions of a balance-task induced changes in gray and white matter architecture (Taubert et al., 2010). These results provide further support for the fast adaptations of the neuronal system in order to deal with a new motor training. Finally, a recent longitudinal study aimed to determine whether the structural adaptations seen in professional musicians when compared to non-musicians are due to training or aptitude prior to training. Using MRI, the authors examined children who choose to participate in instrumental training that began a short time after the tests. Data from this group were compared to a group of children who were not seeking music lessons in foreseeable

future. The baseline-measurement (i.e., starting point of the longitudinal study) did not find any between-group differences in brain structure (Norton et al., 2005). In contrast, significant between-group differences had been found after 15 months of training with the instrumental group showing structural brain changes in music relevant brain areas (Hyde et al., 2009).
Although not a motor training in the proper sense, Draganski and coauthors conducted a further longitudinal study focusing on a cognitive training with a strong association to "real life" learning. Three anatomical images from medical students were collected while the participants learned for a comprehensive examination (i.e., 3 months before examination, shortly after examination, 3 months after examination). Structural changes in gray matter were predominately found in the parietal lobe, indicating that besides motor trainings also an intense cognitive training might induce changes in gray matter architecture. This finding confirms the results of previous studies investigating neuronal adaptations of cognitive trainings (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010; Lustig et al., 2009; Takeuchi, Taki, & Kawashima, 2010).

Functional neuroplasticity

Besides changes in brain anatomy, skill acquisition and training in various domains, such as motor function or cognition, were shown to evoke substantial changes in brain function. One of the first studies that demonstrated the functional correlates of motor learning by means of a longitudinal design was the study from Karni and coauthors (Karni et al., 1995). This study demonstrated a slowly developing increase of neuronal activity in the primary motor area M1 during the course of learning a motor sequence task. Interestingly, this increase of neuronal involvement was only present in a very early stage of training. With a similar task, Hlustik and coauthors demonstrated that after the first two weeks of the sequence learning training the neuronal activation in the sensorimotor cortex reversed and a trend towards a decreased activity became obvious (Hlustik, Solodkin, Noll, & Small, 2004). This finding corroborates well a recent longitudinal motor learning study showing a similar dynamic pattern, namely an increase during the first two weeks of motor learning followed by a decrease during the subsequent two weeks (Ma et al., 2010). Besides affecting the height and extent of neural activations, skill acquisition and learning can also induce a shift of neural activation. In their longitudinal study focusing on the learning of a bimanual task, Debaere and coauthors reported the recruitment of different cortical and sub-cortical motor areas but also a changed laterality (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2004). In accordance with this latter finding, Koeneke and coauthors demonstrated a distinct hemispheric specification during the process of learning (i.e., tapping), in terms of a reduced involvement of the left hemisphere with improved skill level (Koeneke, Lutz, Esslen, & Jäncke, 2006). In contrast, the involvement of the right hemisphere remained stable between the two measurements.
By combining different methods (e.g., structural and functional MRI, TMS), another line of research tried to shed more light on the close relationship of structural and functional

neuroplasticity. For example, Granert and coauthors (Granert et al., 2011) conducted an intervention study with writer cramp patients. The intervention consisted of an immobilization period (4 weeks) followed by a motor training period (8 weeks). First, the gray matter density in the contralateral hand motor area M1 changed depending on the applied intervention type (immobilization or motor training). While the immobilization period was accompanied by a decrease in gray matter, the motor training was associated with an increase in gray matter. Second, in order to understand the functional neuroplasticity that comes along with the structural changes, the authors additionally applied (in addition to the structural MRI) single-pulse TMS to assess the resting motor threshold (RMT) that provides an indication of the motor system excitability. In contrast to the gray matter values, the RMT parameter showed an inverse pattern, with an increase during the immobilization phase and a decrease during the motor training phase. Taken together, the authors concluded that the motor activity measured by RMT might trigger changes in gray matter, hence, indicating the close relationship of structure and function. Furthermore, this study points for both types of neuroplasticity, structural and functional, to the bidirectional characteristic of neuroplasticity. A recent longitudinal study combining structural and functional MRI, provides further support for the close relationship of structural and functional neuroplasticity (Ilg et al., 2008). An essential difference between the two studies was the type of intervention. The latter study examined a two-week cognitive training, namely mirror reading, and not a motor training in the true sense. Besides the training-induced increases in gray matter, also changes (i.e, increases and decreases) in functional recruitment were revealed. The finding that the increase in gray matter was seen in the same area as the increased activity during mirror reading, suggests that the underlying mechanisms base upon synaptic modeling in task relevant regions. However, more research is needed to gain a more comprehensive picture between the close relationship of morphometric and functional changes.

2.2 Motor learning

Motor learning refers to a dynamic process that is strongly related to the repetition of movements in order to achieve a better skill performance. In contrast, less cognitive effort is needed in order to perform the learned and repeated movement pattern (Milton, Small, & Solodkin, 2004). This reduced cognitive effort might for example be reflected in an improved performance or a changed neuronal network. From a classical motor learning perspective, this dynamic process might be sub-divided into two different types, namely *motor sequence learning* and *motor adaptation* (*for reviews see:* Doyon & Benali, 2005; Seidler, 2010). Isolated movements need to be combined in order to execute a coherent and smooth action or behavior during the process of motor sequence learning. Whereas, motor adaption has been defined as the capacity to compensate for changed sensory inputs or motor outputs by adapting single movement parameters, e.g., velocity or force. A plethora of studies has provided strong evidence that this distinct division of motor learning is particularly valid for simple hand or arm movements (Doyon & Benali, 2005; Doyon et al., 2009). These studies have shown that different neuronal networks are involved, depending (a) on the used learning type and (b) on the learning stage (i.e., fast learning, slow learning, and retention) (Doyon & Benali, 2005). However, since the scope of the present dissertation focusses on a highly complex movement, such as playing golf, a clear distinction of the two learning types (motor sequence learning vs. motor adaptation) is not possible. The next subsection focusses on the underlying neuronal mechanisms of motor learning by taking a broader perspective without the clear preference of only one learning type.

2.2.1 Neuronal underpinnings

Since many brain regions contribute to both, motor learning and and motor execution, a precise distinction of these two processes is challenging (Seidler, 2010). Hence, this section refers to a short summary of a wide distributed network of cortical and subcortical regions that are involved during the process of motor learning as well as in controlling motor behaviors. The reader is referred to the following review articles for a more detailed description of the neuronal correlates of the motor system: Doyon & Benali (2005) and Halsband & Lange (2006).

The primary motor cortex (M1)

The primary motor cortex receives mainly afferent input from subcortical regions (ventrolateral and ventroposterior thalamic nuclei) as well as from cortical regions (premotor cortex, supplementary motor area, somatosensory cortex). On the other hand, the corticospinal tract is one of the most important efferent projections from the primary motor cortex via the spinal cord to the muscles in order to produce a movement. Besides the prominent role of the primary motor cortex (M1) in executing movements, this anatomical region has also shown to adapt as a consequence of motor learning. As mentioned above, a slowly developing increase of M1 activation (see 2.1.3) was observed during the

early stages of a sequence learning task (Karni et al., 1995). In contrast, when investigating less complex tasks (i.e., tapping tasks) (Koeneke, Lutz, Esslen, & Jäncke, 2006) or cross-sectional studies with motor experts (i.e., musicians) (Jäncke et al., 2000) M1 demonstrated a reduced involvement. These findings let conclude that variations in M1 activity during the process of motor learning might be related to the neuronal effort needed to execute a task.

Secondary cortical motor areas

The secondary cortical motor areas, including the premotor cortex (ventral and dorsal PMC) and the supplementary motor area (SMA proper and pre-SMA), play a pivotal role in movement preparation. During movement preparation stages, the premotor cortex is considered an important region for the integration of external stimuli (Geyer, 2004). In early learning stages the right PMC showed to be predominantly involved, whereas in later stages, a shift towards the left hemisphere was observed (Serrien, Ivry, & Swinnen, 2006). In addition to this learning stage dependent laterality, the right PMC is also assumed to play a critical role in processing spatial information while preparing for a movement (Ghilardi et al., 2000). Furthermore, the PMC has been repeatedly associated with mental imagination and movement observation (Binkofski & Buccino, 2006; Caspers, Zilles, Laird, & Eickhoff, 2010), both of which represent important strategies of motor skill learning, especially in early stages of the learning process. Concerning motor learning in the more mesial situated SMA regions, a shift from the more anterior pre-SMA towards the SMA proper was observed with progressing skill acquisition (Lee, Chang, & Roh, 1999; Halsband & Lange, 2006). There is strong evidence that the SMA is particularly important to prepare internally guided complex movements in which precise timing and precise selection of movement sequences is needed (Stephan et al., 1999).

Subcortical motor areas

The category of subcortical motor areas include the cerebellum and the basal ganglia. Some main functions of the cerebellum are the on-line correction of errors, the incorporation of feedback information, and the control of speed while performing a movement. This control function of the cerebellum is particularly important at the beginning of the motor learning process. When feedback processes become less important (i.e., in later learning stages) the contribution of the cerebellum decreases. In contrast, the basal ganglia play a pivotal role when a movement is well learned and automatized, i.e., at later learning stages (Ungerleider, Doyon, & Karni, 2002). The basal ganglia are assumed to play a critical role in the initiation and regulation of movements (Berns & Sejnowski, 1998). Furthermore, this structure has been repeatedly shown to play a pivotal role during the process of motor learning, especially when a new motor sequence needs to be learned (Doyon et al., 2009).

Cortical non-motor areas

Besides the "true" motor regions described above also non-motor areas play an important role in order to learn and perform a movement. In respect to motor learning the prefrontal and parietal (inferior and superior) cortices are included in this network. In particular, during the initial stages of learning the prefrontal cortex demonstrated to be involved (Deiber et al., 1997). Attentional, decision, and selection processes were shown to be associated functions of the prefrontal cortex while learning a new movement (Jueptner et al., 1997). Concerning the parietal lobe, there are two main motor learning functions. First, the rostral part of the inferior parietal lobe has been suggested to be important in planning goal-oriented actions (Tunik, Lo, & Adamovich, 2008), particularly with respect to the integration of multimodal information (Eickhoff et al., 2010). Second, the more caudal part of the inferior and superior parietal lobes are functionally and anatomically connected to the visual system (Colby & Goldberg, 1999; Culham, Cavina-Pratesi, & Singhal, 2006) and belong to the dorsal stream. They are especially important for a precise transformation from visual stimuli into a motor command and coding of spatial information.

2.2.2 Transfer effects of motor trainings

So far, longitudinal motor learning studies have paid little attention to the assumption that motor trainings might trigger transfer effects onto cognitive functions. Studies that investigated a motor training in terms of a physical activity, rather than a motor learning study in the true sense of the word, have indicated a beneficial effect of the motor training on brain function and cognition. Consistent effects of physical activity on cognition were observed particularly in older adults (Hillman, Erickson, & Kramer, 2008). Previous studies indicate a broad effect onto a wide range of cognitive functions (e.g., sensory discrimination, spatial abilities, mental speed). In an analogous manner there is evidence that the beneficial effect of a cardiovascular training is particularly strong on executive control processes (Colcombe & Kramer, 2003; Kramer, Erickson, & Colcombe, 2006; Verghese et al., 2003; Voelcker-Rehage, Godde, & Staudinger, 2010). In an intervention study with participants older than 60 years, Colcombe and coauthors demonstrated that the neuronal activation while performing flanker task (i.e., a task examining the executive functions) is affected by the level of physical fitness (Colcombe et al., 2004). The applied intervention was a regularly performed aerobic training (three times per week) for a duration of six months, and the neuronal correlates of the flanker task were measured by means of fMRI. The authors suggested that the increased physical fitness may go along with a more efficient attentional neuronal network, and thus, less effort might be needed to process a cognitively challenging task. In a further MR-based neuroanatomical study, the same group showed that physical fitness correlates positively with gray matter volumes in those regions of the brain that show greatest age-related declines (frontal, prefrontal, and parietal cortices) in humans (Colcombe et al., 2006).

2.2.3 Motor training characteristics

As described in the sections above, it has been shown that distinct motor trainings may induce neuroplasticity or even transfer effects to non-trained cognitive functions. However, to date there is little knowledge about the requirements and characteristics of a motor training. Previous studies investigating neuronal and cognitive training effects vary widely with respect to practice characteristics, such as duration and intensity. While it has been shown that motor trainings induce learning related changes - in terms of changed anatomical parameters (Draganski & May, 2008), changed functional parameters (Hlustik et al., 2004), or cognitive parameters (Noack, Lövdén, Schmiedek, & Lindenberger, 2009) - so far only very few studies have compared different training parameters with respect to their impact on neural plasticity (Studer, Koeneke, Blum, & Jäncke, 2010). In the motor domain, the existing longitudinal training studies in healthy subjects attached great importance to controlled training situations – keeping constant as many training parameters as possible (e.g., training duration per day, overall training duration, training schedule, strategies, etc.). The neural effects of a training that is performed aside from strict experimental control – for instance as a true leisure activity – are not yet studied. Considering that the participation in leisure activities was shown to influence the process of brain aging and the risk to develop dementia (Colcombe et al., 2006; Verghese et al., 2003), it is important to extend previous research by focusing on trainings that approximate the real-life situation and, therefore, possess higher ecological validity.

2.2.4 Motor learning and age

Coordination, timing, balance and consistent actions, represent important functions in order to learn a new movement. A great amount of work has shown that these functions decline with age, in terms of coordination difficulties (Seidler, Alberts, & Stelmach, 2002), slowing (Diggles-Buckles, 1993), greater movement variability (Contreras-Vidal, Teulings, & Stelmach, 1998), balance difficulties and gait difficulties (Woollacott & Tang, 1997). Although these age-related constraints exist, recent research provides strong evidence that older adults are also able to learn new motor skills, such as juggling (Boyke et al., 2008) or a sequence learning task (Seidler, 2006). However, the underlying neuronal mechanisms of motor learning have been shown to change as consequence of aging. In order to compensate (see 2.1.2) for the age-related sensorimotor constraints, older participants showed a pronounced role of cognitive motor control processes and a reduced involvement of automatic control processes (Wu & Hallett, 2005). Thus, the increased involvement of the prefrontal region has been suggested to function as a compensatory process, while older adults perform a motor task. However, in contrast to this compensatory capacity the same brain region is at the same time highly vulnerable to age effects, meaning that this compensation process reaches also its limits (Seidler et al., 2010). Consequently, in the prefrontal cortex there exist two opposed processes, a “positive” compensation process and a counteracting age effect.

Despite the fact that age influences motor control processes, motor learning, and the

underlying neuronal mechanisms - many questions still remain unanswered. As an example of this, it is (a) unclear when such compensation processes start and (b) how interventions might support compensatory processes or (c) counteract age-related declines in motor control.
Behavioral studies were able to show that substantial differences in terms of age-distinct learning curves exist in the process of motor learning, both for elderly (Verwey, 2010) and the middle age cohort (Verwey, Abrahamse, Ruitenberg, Jimenez, & de Kleine, 2011). However, the question regarding the neuronal underpinnings of motor learning in middle age participants - meaning participants between the age of 40 and 60 years - has not been addressed so far.

2.2.5 Motor imagery

The main aim for the second study of this dissertation was to study the functional correlates of golf training. Due to space constraints of the MR-tomography the investigation of a real golf movement is infeasible. Therefore, a motor imagery task was conducted. Motor imagery is defined as the mental rehearsal of movements without overt execution (Solodkin, Hlustik, Chen, & Small, 2004). As has been shown by previous studies (Milton, Small, & Solodkin, 2008; Munzert, Lorey, & Zentgraf, 2009), motor imagery provides an alternative approach to investigate the neuronal underpinnings of broad movements involving several body parts.
Different lines of research focused on the close relationship of overt movements and motor imagery (Decety & Ingvar, 1990; Pascual-Leone et al., 1995; Roland, Eriksson, Stone-Elander, & Widen, 1987). From a theoretical point of view, Jeannerod (2001) proposed that motor imagery and motor execution share the same neuronal representations and he termed this theory "the simulation theory". This theory suggests that each executed movement bases on an underlying cognitive component. Jeannerod (2001) termed the underlying cognitive component *S-states* and suggested that this stage differed only by an executive component from overt movements. It should be remarked that imagined as well as observed movements fall into the S-states category (i.e., covert movements). Referring to this theory and concerning the neuronal correlates, a covert movement resembles the simulation of an overt (i.e., executed) movement. Thus the motor representation of simulated movements includes not only motor plans but also the intended motor actions (Olsson & Nyberg, 2010). In order to test Jeannerod's theory, but also to investigate the neuronal correspondence of imagined and executed movements, previous neuroimaging studies used mainly simple motor tasks. These studies demonstrated a strong overlap between imagined and executed movements and, therefore, provide support for the theoretical idea of Jeannerod (Gerardin et al., 2000; Lotze & Halsband, 2006). A neuronal overlap between executed and imagined movements was found mainly in the following brain regions: secondary cortical motor areas (ventral and dorsal premotor cortex PMC, supplementary motor area SMA), subcortical motor areas (basal ganglia), cerebellum, and parietal cortex (superior parietal lobule and intraparietal sulcus). The activation peaks of the frontal regions (i.e., PMC, SMA) showed to be located more anterior in

imagery conditions compared to execution conditions. Concerning the parietal cortex a reversed pattern, with more posterior regions during imagery was shown (Gerardin et al., 2000). In contrast, the involvement of the primary motor cortex M1 during the process of imagination is still unclear. While some studies reported M1 activation during motor imagery (Lotze, Montoya, Erb, & Hülsmann, 1999; Porro, Cettolo, Francescato, & Baraldi, 2000) others failed to demonstrate the involvement of M1 while mentally rehearsing a movement (Binkofski et al., 2000; Hanakawa et al., 2003). One explanation for this inconsistencies originates from neuroimaging studies using the method of functional connectivity. These studies suggested that the lack of M1 during imagery, may be explained by the suppressive influence of SMA on M1 (Kasess et al., 2008; Solodkin et al., 2004).

Recent research indicates that the requirements as well as the neuronal underpinnings may differ in respect to the type of motor imagery (Guillot et al., 2009). Motor imagery may be subdivided in two different modalities or perspectives, respectively - either an internal (i.e., first-person, kinesthetic motor imagery) perspective or an external (i.e., third-person, visual motor imagery) perspective. The neuronal recruitment patterns of these two perspectives are similar but not identical. In particular, the kinesthetic imagination of movements from a first-person perspective showed a striking overlap with executed movements (sensorimotor system, parietal lobe) (Guillot et al., 2009). During a kinesthetic motor imagery condition participants are asked to "feel the movement". In contrast, the external motor imagery perspective, which requires visualization skills, was strongly associated with regions processing visual information, such as the occipital lobe and the parietal lobe.

Besides distinct condition characteristics of motor imagery onto the underlying neuronal networks, there is also strong evidence that the level of expertise affects the imagery of movements. Generally, a lower skill level (Godde & Voelcker-Rehage, 2010; Lacourse, Orr, Cramer, & Cohen, 2005; Milton et al., 2007; Olsson, Jonsson, Larsson, & Nyberg, 2008; Ross, Tkach, Ruggieri, Lieber, & Lapresto, 2003) or a poorer imagery competence (Guillot et al., 2008) go along with an extended neuronal recruitment pattern. These findings suggest that motor experts or participants with a higher imagery performance need less effort in order to perform the imagery task and, thus, might have additional resources for cognitive control processes (e.g., additional attentional processes). In summary, not only the neuronal recruitment patterns but also expertise effects resemble between kinesthetic motor imagery and overt movements.

Due to strong overlap of kinesthetic motor imagery and movement execution this task provides an alternative approach to study training-induced functional neuronal plasticity. However, the research to date focused mainly on cross-sectional study designs, and thus it is unclear whether training-induced neural adaptations in novices, as studied in longitudinal designs, can be revealed using the approach of mental imagery.

3 Methods

3.1 Study sample

There is strong evidence that training-induced neuronal plasticity is a dynamic process of the nervous system that is not restricted to a single developmental stage but rather encompasses the entire lifespan (Freitas et al., 2011). A great amount of work has been delineated to either a young (i.e., aged younger than 30 years) study population (Hyde et al., 2009) or older participants (i.e., aged 65 or older) (Lustig et al., 2009). These previous studies have shown that age may be regarded as a crucial factor, in particular influencing the magnitude of training-induced plasticity (Boyke et al., 2008). However, participants in the middle adulthood have often been neglected, not only in the domain of training-induced plasticity, but also in overall neuroscientific research. Therefore, it is indispensable to study this age cohort in more detail in order to understand the influence of age on the magnitude of neuroplasticity.

Besides the criterion of age, an additional inclusion criterion was the beginning of a complex motor training. By using a complex motor task, this dissertation tried to extend previous studies investigating structural and functional plasticity that used simple motor tasks, such as finger tapping (Doyon & Benali, 2005; Koeneke, Lutz, Herwig, Ziemann, & Jäncke, 2006). Furthermore, we decided to use a complex motor task that can be practiced as a leisure activity in order to increase ecological validity in the present project. In fact, the drop-outs might be reduced by an increased ecological validity and a leisure activity respectively. The problem of drop-outs are a central issue when conducting a longitudinal study for a longer time period lasting more than a few weeks. Additionally, a leisure activity goes along with increased motivation and reduced training irregularities.

The experimental group (n=17) of the present dissertation consists of golf novices between the age of 40 and 60 years. Learning to play golf puts high demands on coordinative skills and attentional processes. Thus this leisure activity conforms to both above mentioned criteria, i.e., *age* and a *complex motor task*. Additionally, this physical activity can be practiced in all age groups and starting to play golf is not restricted to a certain age group. This age independency has the consequence that also people in the middle adulthood start to play golf as a leisure activity. In addition to data from the golf novice group, data from a passive (n=18) and an active (n=15) control group were collected. The active control group started with a nordic walking training. Nordic walking is a leisure activity that strengthens the cardiovascular system without imposing high demands on coordinative skills and concentration. Participants from the passive control group were only included in the present study if they did not have any golf or

nordic walking experience and did not start with a new physical workout during the study period. None of the participants, irrespective of the group, had any history of neurological or psychiatric disorder. All subjects gave written informed consent and the local ethics committee approved the present dissertation in compliance with the Helsinki Declaration.
The two studies included in this present dissertation (see empirical part) correspond to data from a sub-sample of 11 participants of the golf group (9 women, 2 men) and from 11 participants of the passive control group (9 women, 2 men) with a mean age of 51.2 (SD=7.2). The reason for this sub-sample was that 6 out of 17 golf novices did not continue with the golf training during study participation and thus had to be defined as drop-outs. The two groups were matched for age, hand and sex. Handedness was verified by means of the Annett Handedness questionnaire (Annett, 1970). According to this test, 20 participants (10 golf group, 10 control group) were classified as consistent right-handers and 2 participants as consistent left-handers.

3.2 Experimental design

The present dissertation investigated training-induced anatomical and functional neuronal plasticity by means of a longitudinal experimental design. For the golf group, data from two (T1, T2) measurement time-points were collected (see Figure 3.1). The inter-measurement interval between T1 and T2 amounted to 40 training hours. The two control groups (i.e., nordic walking group and passive control group) run through data collection of two measurement time-points. The inter-measurement interval for the nordic walking group amounted to 40 nordic walking training hours. The nordic walking group needed a mean duration of 211 days to achieve this criterion. The inter-measurement interval for the passive control group corresponded to the inter-measurement interval (duration between T1 and T2) of the golf group, i.e., mean time needed to achieve 40 training hours. Thus, the control group's interval amounted to a mean duration of 150 days.
The reason for referring the inter-measurement interval onto a certain amount of training hours, and not to a distinct number of weeks, bases on the training characteristics of the investigated interventions. For both intervention groups, golf and nordic walking, we preconditioned that the participants begin either to play golf or to workout nordic walking as a leisure activity. In contrast to previous studies with very well controlled training situations (Draganski et al., 2004; Taubert et al., 2010), the present dissertation, including leisure activities as intervention, comes along with highly individual training routines. The golf and nordic walking training hours were recorded on a training log. Each golf participant logged its own training routine on the training log, indicating the duration and the kind of training (driving ranch, golf course, with or without golf pro, etc.). The nordic walking participants recorded training-duration, training intensity (4 scales from low to high intensity), and any additional cardiovascular training.
The two studies presented in the empirical part (see chapter 5) focus on data of the two measurement time-points, namely T1 and T2 of the golf group and T1 and T2 of the

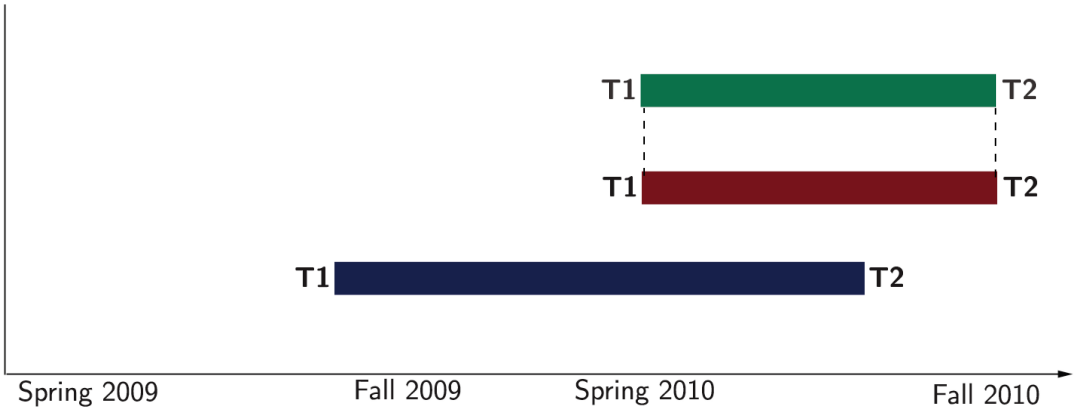

Figure 3.1: Experimental design with the measurement time-points (T1, T2) and the three groups (golf group = green; control group = red; nordic walking group = blue).

control group. For the golf group the interval between the two measurements amounted to 40 golf-training hours. Each golf novice had its individual inter-measurement interval, calculated on the basis of the training hours, recorded on the training log. In addition to the standard matching variables (age, sex, handedness) we also ensured that the two groups had the same mean inter-measurement interval.

3.3 Voxel-based morphometry as a method to study structural neuroplasticity

The method of voxel-based morphometry (VBM) was applied in order to investigate morphometric changes induced by the physical training. This method enables the segmentation of the T1-weighted MR-images into different tissue classes, i.e. gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) segments. Before analyzing the high-resolution 3-D anatomical images, the following pre-processing steps were required:

1. Registration of T2 scan to T1 scan for each subject separately.
2. Intra-subject bias correction.
3. Segmentation of the different tissue classes by accounting for partial volume effects (Tohka & Zijdenbos, 2004), by applying adaptive maximum a posteriori estimations (Rajapakse, Giedd, & Rapoport, 1997), and by applying a hidden Markov random field model (Cuadra, Cammoun, Butz, Cuiseanaire, & Thiran, 2005).
4. Linear (i.e. affine) and non-linear normalization (i.e. Dartel).
5. Smoothing with an 8 mm width at half maximum (FWHM) Gaussian kernel.

An adapted pre-processing routine was needed (1. and 2. in the list of pre-processing steps) with respect to the longitudinal study design, before the longitudinal pre-processing

routine of the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) could be performed. The VBM8 toolbox is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2010a (Mathworks Inc., MA, USA).
Subsequent to the pre-processing procedure, a voxel-wise comparison of the gray-matter values between groups - or in the present dissertation also between the two time-points - was possible. The statistical analysis of the gray matter segments was performed by means of a repeated-measures ANOVA (i.e., flexible factorial model in SPM8) with within-subject factor time (T1, T2) and between-subject factor group (golf group, passive control group). Threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) was used to detect significant clusters. This approach provides the ability to perform cluster-based inference without the need to initially specify a cluster-forming threshold. Due to two reasons additional regions-of-interest (ROI) -analyses were performed. First, a ROI-based interaction analysis ascertained that the changes in gray matter were exclusively ascribed to the golf group and not to the control group. Second, this approach permitted to investigate the relationship between morphological changes and behavior (e.g., training intensity of the golf group) in more detail.

3.4 Functional magnetic resonance imaging as a method to study functional neuroplasticity

In order to study functional changes related to the golf training, the method of functional magnetic resonance imaging (fMRI) was applied. Due to the strong relationship of neural activity, in terms of local field potentials, and neurovascular properties (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), it is possible to measure "neural activity" or more precisely the hemodynamic response that is related to a certain task. However, due to technical reasons it is not possible to measure the "direct" neural activity by means of the MRI-technique. To solve this problem, the "indirect" neural activity, i.e., the hemodynamic response, provides an alternative approach. This alternative makes use of the influence of blood onto inhomogeneities in the magnetic field due to O_2 changes in the blood while performing a task (Ogawa, Lee, Kay, & Tank, 1990). This influence is used as contrast and is termed as the BOLD (Blood Oxygenation Level Dependent) signal. A higher MR-signal onto the T2*-weighted images is caused by a relative decrease of de-oxyhemoglobin, which in turn possesses paramagnetic properties (Jäncke, 2005). In other words, when a brain region is neurally activated the supply of oxygenated blood is higher as the actual need and, subsequently, the relative de-oxygenated blood decreases. By means of modern fMRI techniques a good spatial resolution (approximately 2-3 mm) is achieved. On the other hand the temporal resolution of the BOLD-signal are poorer (in the range of seconds), especially when referencing to alternative methods, such as EEG (electroencephalography; temporal resolution in the range of ms) (Jäncke, 2005).
Like the anatomical data, the fMRI-data needed to be pre-processed first. The following procedures were applied:

1. Realignment to the first volume in order to correct for movement artifacts.
2. Normalization to the standard stereotactic space (EPI template provided by the Montreal Neurological Institute).
3. Smoothing with a Gaussian kernel of 8mm full-width-at-half-maximum.

Activated voxels were identified by the general linear model approach, implemented in SPM8 software. In a first step we aligned for each participant a model with the different test sessions (i.e., measurement sessions), the different experimental conditions and six movement regressors (with the realignment parameters). This facilitated an estimation of the overlap between the task-predictions from the aligned model and the data (i.e., hemodynamic response). In a second step, random effect analysis were applied in order to permit population-level inferences. Finally, maps of contrast coefficients of the first level were collectively submitted to analyses of variance (ANOVAs) for repeated measures (i.e., flexible factorial model in SPM8).

4 Aims and research questions

The primary aim of this dissertation was to assess training-induced changes of brain anatomy and brain function in golf novices in middle adulthood. The motivation for this main aim bases on previous research investigating the neuronal underpinnings of motor training-induced neuroplasticity. These previous studies provided major insights about neuronal mechanisms of motor learning and the great capacity of the brain to adapt quick and efficiently to a broad variety of environmental factors.

By reviewing the pertinent research of motor-training induced neuroplasticity the following two research gaps emerged. First, although training-induced neuroplasticity has been acknowledged as a process occurring throughout the whole life-span, the neuronal underpinnings of training-induced adaptations in subjects in the middle adulthood, i.e., participants between the age of 40 and 60 years, have received little scientific attention. Second, although a few previous longitudinal studies shed more light on the dynamic aspects of motor learning, there remain many interesting open questions. For example, it has been repeatedly shown that strict and controlled training protocols might induce structural and functional neuroplasticity. Considering, however, that the participation in leisure activities was shown to influence the process of brain aging and the risk to develop dementia, it is important to extend previous research by focusing on trainings that approximate the real-life situation and, therefore, possess higher ecological validity. Furthermore, we are convinced that only a longitudinal study design possess the potential to address this issue.

This dissertation, which aligned a longitudinal study design and used the methods of structural and functional MRI, includes two studies. The first study focussed on changes of gray matter induced by the golf-training, whereas the second study focussed on changes of functional neuronal recruitment patterns while mentally performing a golf swing.

Consequently, the following principal research questions and its associated hypotheses were addressed:

1. How do neuroanatomical parameters change in golf novices that absolve a 40 hour golf-training performed as a leisure activity with highly individual training protocols?

→ Given the complexity of learning to play golf, we expected a practice-induced gray matter increases in an extended neural network encompassing regions of the entire dorsal stream (Culham et al., 2006) known to play a pivotal role in serving visuomotor skills, regions typically associated with motor learning (i.e. sub-cortical and cerebellar motor areas) as well as frontal associative regions concerned with

more cognitive aspects of motor skill acquisition (Doyon & Benali, 2005).

2. What are the neuro-functional recruitment patterns of golf novices and control subjects during motor imagery of a golf swing at baseline?

→ We expect an extended network to be associated with the mental rehearsal of a golf swing, including sensorimotor regions and the dorsal stream.

3. Does the 40 hours golf training affect the neuro-functional recruitment patterns evolving during the mental imagery of a golf swing?

→ We expect changes of neural activity between the two measurement time-points within task-relevant regions that are limited to the golf novice group.

4. Does a training with a high ecological validity, i.e., a leisure activity, show similar neuroanatomical effects as a training under strict experimental control?

→ Due to the lack of pertinent research, this question can only be addressed in an exploratory way.

5 Empirical Part

5.1 Training-induced structural plasticity in golf novices

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5.1.1 Abstract

Previous neuroimaging studies in the field of motor learning have shown that learning a new skill induces specific changes of neural gray and white matter in human brain areas necessary to control the practiced task. Former longitudinal studies investigating motor skill learning have used strict training protocols with little ecological validity rather than physical leisure activities, although, there are several retrospective and cross-sectional studies suggesting neuroprotective effects of physical leisure activities. In the present longitudinal magnetic resonance imaging (MRI) study, we used voxel-based morphometry to investigate training-induced gray matter changes in golf novices between the age of 40 and 60 years, an age period when an active life style is assumed to counteract cognitive decline. As a main result, we demonstrate that 40 hours of golf practice, performed as a leisure activity with highly individual training protocols, are associated with gray matter increases in a task-relevant cortical network encompassing sensorimotor regions and areas belonging to the dorsal stream. A new and striking result is the relationship between training intensity (time needed to complete the 40 training hours) and structural changes observed in the parieto-occipital junction. Thus, we demonstrate that a physical leisure activity induces training dependent changes in gray matter and assume that a strict and controlled training protocol is not mandatory for training-induced adaptations of gray matter.

5.1.2 Introduction

The human brain demonstrates an enormous capacity to adapt – quickly and efficiently – to a broad variety of environmental demands. Amongst others, skill acquisition and training in various domains, such as motor function or cognition, were shown to evoke substantial changes in brain anatomy (Jäncke, 2009). Moreover, research of the last decade provides strong evidence that these training-induced changes occur across the entire lifespan – from birth to old age (Lustig et al., 2009; Seidler, 2007).
The neuroanatomical underpinnings of proficient motor skills have been initially studied in highly trained motor-experts (e.g., professional musicians) applying cross-sectional study designs. From these studies one can conclude that skill acquisition or performance improvement induces specific structural changes in brain areas demanded by the practiced task (Gaser & Schlaug, 2003; Hanggi et al., 2010; Jäncke et al., 2009). Recent longitudinal neuroimaging studies focused on the impact of motor trainings lasting several days or weeks in untrained subjects and showed adaptations in both, neural gray (Draganski et al., 2004; Driemeyer et al., 2008) and white matter (Scholz et al., 2009; Taubert et al., 2010). However, longitudinal studies investigating training-induced changes in anatomical properties of the cortical motor system are rare, particularly in older age groups. As a consequence there is little knowledge about the extent of the neural changes and factors influencing it, such as age (Boyke et al., 2008) or certain training characteristics (e.g., intensity or duration). In the motor domain, the existing longitudinal training studies in healthy subjects attached great importance to controlled training situations – keeping constant as much training parameters as possible (e.g. training duration per day, overall training duration, training schedule, strategies, etc.). The neural effects of a training that is performed aside from strict experimental control – for instance as a leisure activity – are not yet studied. Considering, however, that the participation in leisure activities was shown to influence the process of brain aging and the risk to develop dementia (Colcombe et al., 2006; Verghese et al., 2003), it is important to extent previous research by focusing on trainings that approximate the real-life situation and, therefore, possess higher ecological validity.
Consequently, the present study was designed to explore training-induced neural adaptations in golf novices performing their regular golf practice aside from strict experimental control in the setting of their specific golf clubs. Since our knowledge about neural plasticity is particularly limited when it comes to the middle adult age, we recruited subjects between the age of 40 and 60 years. The main focus was on changes of neural gray matter, which can be ascribed to the golf practice. Given the complexity of learning to play golf, we expect a practice-induced gray matter increase in an extended neural network encompassing regions of the entire dorsal stream (Culham et al., 2006) known to play a pivotal role in serving visuomotor skills, regions typically associated with motor learning (i.e. sub-cortical and cerebellar motor areas) as well as frontal associative regions concerned with more cognitive aspects of motor skill acquisition (Doyon & Benali, 2005).

5.1.3 Methods

Subjects:
22 healthy volunteers (18 women, 4 men), with a mean age of 51.2 (SD=7.2) years participated in the present study. None of the participants had any history of neurological or psychiatric disorder. The study sample consisted of the following two groups, a golf novice group (n=11; 9 women, 2 men) and an age- and sex-matched passive control group (n=11) meaning that no specific training was applied in this group. Handedness was verified by means of the Annett Handedness questionnaire (Annett, 1970). According to this test, 20 participants (10 golf group, 10 control group) were classified as consistent right-handers and 2 participants as consistent left-handers. Control participants were only included in the present study if they did not have any golf experience and did not start with a new physical workout during the study period. All subjects gave written informed consent and the local ethics committee approved the present study, in compliance with the Helsinki Declaration.

Experimental design:
We used a longitudinal study design with two measurement time-points. At each measurement time-point, a T1-weighted image was recorded from each participant. The golf group had approximately 77 hours of golf pre-experience. The interval between the two measurements referred to the golf group and amounted to 40 golf-training hours. Each golf novice has its individual inter-measurement interval, calculated on the basis of the training hours, recorded on a training log. Accordingly, we inferred the training intensity (TI) from the elapsed time to achieve 40 training hours by using the following formula: TI = 40/(x days for 40 training hours). Since each participant of the golf group was matched (age, sex, handedness) to a participant of the control group, we ensured that the two groups had the same inter-measurement interval.

MRI data acquisition:
The MRI data were acquired on a 3T Philips Intera whole-body magnetic resonance tomograph equipped with an eight-channel Philips SENSE head coil. Whole brain anatomical images were obtained from 160 slices by using a T1-weigthed three-dimensional gradient echo pulse sequence (turbo field echo TFE). The following acquisition parameters were used: repetition time TR = 8 ms, echo time TE = 3.7 ms, flip angle = 8°, field of view FOV = 240 x 240, slices = 160, spatial resolution = 0.94 x 0.94 x 1 mm^3.

Voxel-based morphometry:
Data preprocessing and analysis was performed with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2010a (Mathworks Inc., MA, USA). We applied the default longitudinal preprocessing approach integrated into the VBM8 toolbox. For this purpose, the following preprocessing steps were required: (1) registration of time-point 2 scan to time-point 1 scan for each subject separately,

(2) intra-subject bias correction, (3) segmentation of the different tissue classes, (4) linear (i.e., affine) and non-linear registration (i.e., Dartel), (5) modulation of the different tissue segments by the non-linear normalization parameters in order to account for individual brain size differences. The segmentation procedure was further refined by accounting for partial volume effects (Tohka & Zijdenbos, 2004), by applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997), and by applying a hidden Markov random field model (Cuadra et al., 2005). Finally, the realigned and normalized gray matter segments were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel.

Statistical analysis:

First, we performed a repeated-measures ANOVA (i.e., flexible factorial model in SPM8) with within-subject factor time (T1, T2) and between-subject factor group (golf group, control group). We were particularly interested in increases and decreases in gray matter intensities of the golf group. In order to ascertain that gray matter increases seen in the golf group can exclusively be ascribed to the golf training, we performed an additional interaction analysis. This analysis bases on regions-of-interest (ROIs) extracted from the clusters showing a gray matter increase in the golf group.

In a second step, we performed a ROI analysis to analyze the training-related structural changes in more detail. Accordingly, we created spherical ROIs with a radius of 8 mm by using the marsbar tool (http://marsbar.sourceforge.net/). The center coordinates were defined by the local maxima of the whole brain analysis, i.e., the significantly increased gray matter regions of the golf group. We calculated for each golf participant and each ROI the percent increase in gray matter intensity. As a result, for each ROI a regression analysis with the predictor training-intensity (TI) and the dependent variable percent increase in gray matter was performed.

Threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) was used to detect significant clusters. This approach provides the ability to perform cluster-based inference without the need to initially specify a cluster-forming threshold. For each analysis, 5000 randomization runs were performed. Statistical maps were thresholded at $p < 0.05$ corrected for the entire search volume.

5.1.4 Results

Behavioral data

The golf and control group did not differ in age and education (both $p>0.1$). The golf-training group needed a mean duration of 149.82 days (range: 92-235 days) to achieve 40 training hours. Accordingly, the mean training intensity (TI), defined as the ratio TI=40h/d, was 0.295 (SD=0.096). Furthermore, participants who passed the basic entrance examination "license to play on golf courses" successfully, practiced with a considerable higher intensity (*Cohen's d*=2.60). Hence, this subgroup (n=4) needed less time to achieve 40 training hours.

Main contrast "post-pre-training" in the golf group

In line with our hypotheses the golf novices revealed increased gray matter values in areas associated with the dorsal stream and critical regions in the process of motor learning (Figure 5.1, Table 5.1). In the process of the golf training, increases were found in the ventral part of the central sulcus encompassing both the motor and sensory compartment (M1, S1). A further region of gray matter increase is situated in the vicinity of the ventral premotor cortex (PMC) and the inferior frontal gyrus. Additionally, regions belonging to the left and right inferior parietal lobe showed training-induced increases in gray matter. In contrast, the other tests investigating differences between the two time-points (i.e., decreases in the golf group, increases and decreases in the control group) and between the two groups at baseline did not differ with respect to gray matter.

Table 5.1: Significant gray matter changes in the golf group

No.	**Anatomical area**	**Hem.**	**MNI**			**Inc. golf**	**Interaction**
			x	y	z	*p*	*p (Cohen's d)*
1	Central sulcus	L	-62	-4	25	.037	.001 (2.24)
2	Ventral PMC	L	-58	11	21	.046	.001 (1.87)
3	Rostral IPL	L	-58	-43	25	.049	.001 (1.62)
4	Rostral IPL	L	-50	-19	24	.040	.001 (1.68)
5	Rostral IPL	L	-46	-45	33	.043	.003 (1.47)
6	Intraparietal sulcus	L	-27	-67	28	.050	.012 (1.18)
7	POJ	R	21	-85	30	.046	.001 (1.64)
8	Caudal IPL	R	38	-72	19	.043	.009 (1.24)
9	Caudal IPL	R	36	-63	34	.042	.380 (.38)

Significant gray matter changes in the golf group between the two measurement time points (increases in the golf group). All results are corrected for the entire search volume. The coordinates (x, y, z) correspond to the MNI-coordinate system. Last column refers to the p-value (Bonferroni corrected) and the effect size (*Cohen's d*) of the interaction (Group x Time). The consecutive indices 1 – 9 relate to the numbers used in Figure 5.1 and Figure 5.2 .

Interaction contrast "group x time-point"

The interaction analysis confirmed the increased gray matter changes of the golf group.

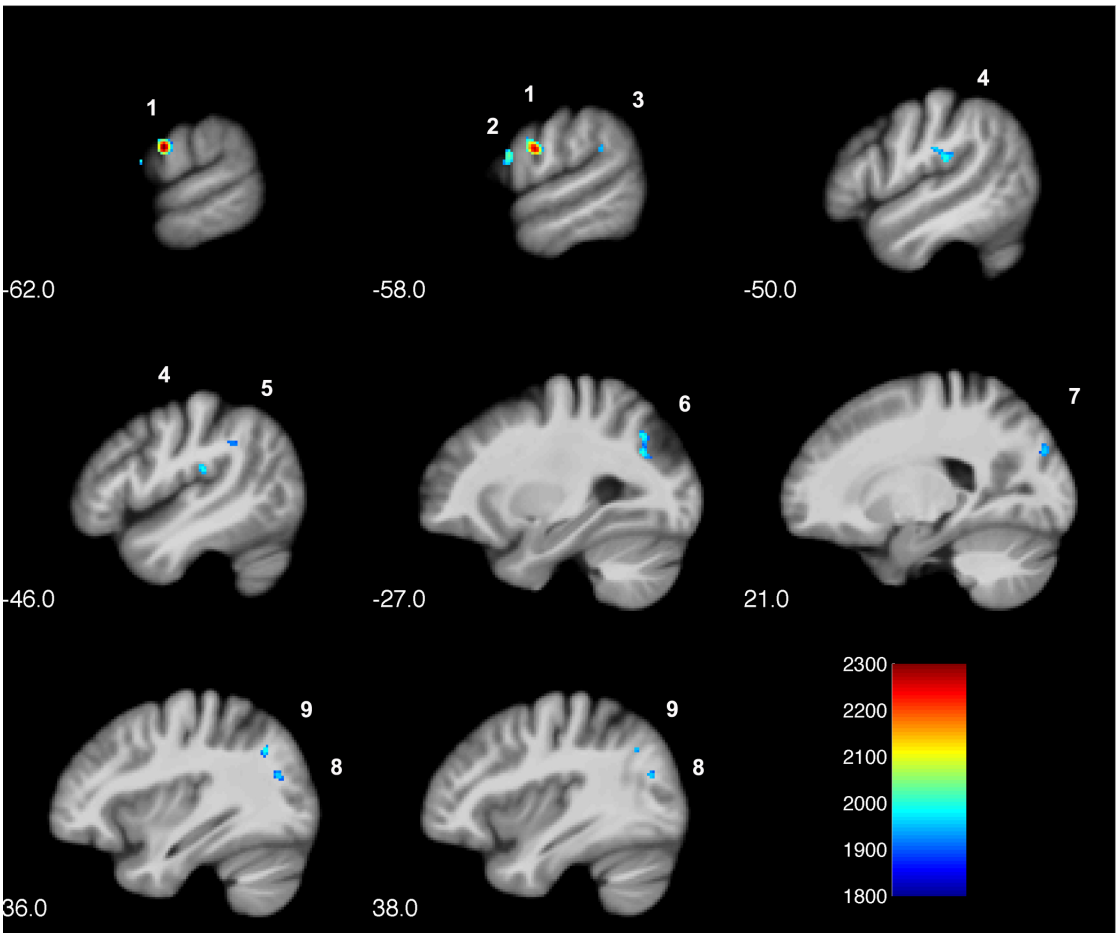

Figure 5.1: Gray matter increases (sagittal slices with x coordinate value) in the golf group: (1) central sulcus, (2) ventral premotor cortex, (3) rostral inferior parietal lobule, (4) rostral inferior parietal lobule, (5) rostral inferior parietal lobule, (6) intraparietal sulcus, (7) parieto-occipital junction, (8) caudal inferior parietal lobule, (9) caudal inferior parietal lobule. The color bar represents the TFCE-statistics.

While gray matter increases in the golf group were prominent in all tested regions, gray matter increases were absent or greatly reduced in the control group (Figure 5.2). Table 1 contains the p-values (Bonferroni-corrected by applying the procedure suggested by Holm; Holm, 1979) and the effect sizes (*Cohen's d*) of the associated interaction effects. We would like to emphasize that all results remained stable in terms of effect sizes even if the two left-handers were excluded from the analyses.

Regression analysis

In order to assess the influence of training-intensity on gray matter changes, we performed a region-of-interest (ROI) analysis. This analysis revealed a strong relationship (r=0.83) between training-intensity and percent increase in the right parieto-occipital junction (POJ) (Figure 5.3). As can be seen from Figure 5.3, there is a clear trend that the golf novices with the license to play golf courses showed larger changes in this ROI compared to the golf novices without this license (*Cohen's d*=1.41). Furthermore, we see a trend for a relationship between training-intensity and percent increase in the

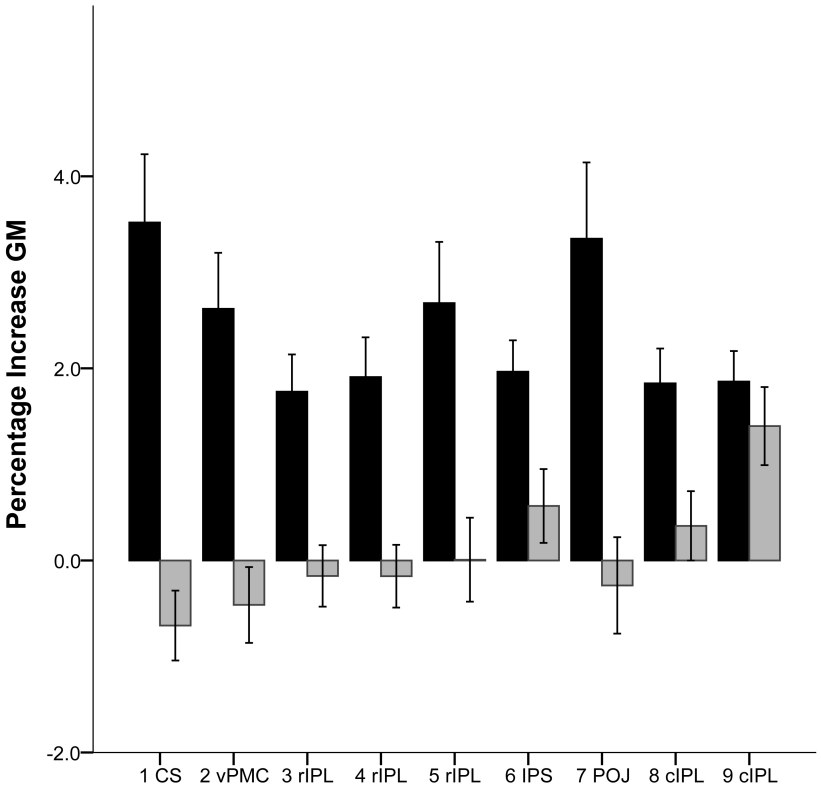

Figure 5.2: Interaction effects for changes in gray matter between the golf (black) and the control (gray) group: (CS) central sulcus, (vPMC) ventral premotor cortex, (rIPL) rostral inferior parietal lobule, (IPS) intraparietal sulcus, (POJ) parieto-occipital junction, (cIPL) caudal inferior parietal lobule. Error bars represent 1 standard error.

ventral premotor cortex (r=0.56).

5.1.5 Discussion

Based on former research, we hypothesized that the golf novice group will demonstrate training-induced adaptations in gray matter in brain regions demanded by the golf training. Two main findings of the present study provide support for this hypothesis. First, we show that 40 hours of golf training induce an increase in gray matter in task-relevant cortical regions encompassing sensorimotor regions and areas belonging to the dorsal stream. Second, structural adaptations in the right parieto-occipital junction (POJ) were strongly related to the intensity of training.

Our results are in good agreement with previous longitudinal studies demonstrating fast macroscopic changes of gray and white matter induced by a motor training (Driemeyer et al., 2008; Taubert et al., 2010). However, a new and striking result is that the training-induced gray matter changes observed in our study are not dependent on strict training or experimental constraints. Previous studies investigating training-induced neuronal

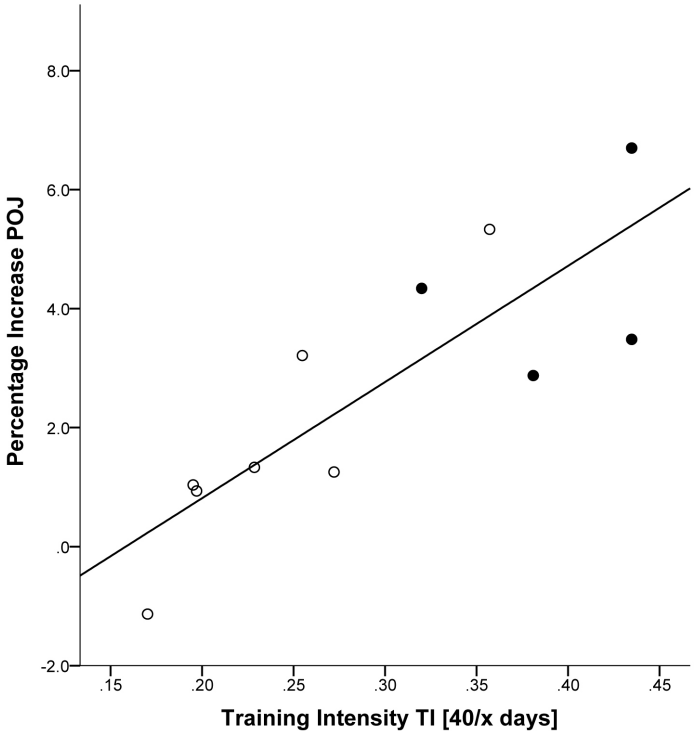

Figure 5.3: Correlation of gray matter percent increase in the parieto-occipital junction (POJ) and training intensity (TI). Filled dots represent golf participants who passed the basic entrance examination within the study period.

plasticity attached great importance to keep training parameters constant across subjects in order to optimize effect strengths (Lustig et al., 2009). On the other hand, cross-sectional behavioral studies indicate a beneficial effect of certain leisure activities, such as dancing or playing chess, onto the risk to develop dementia (Rovio et al., 2005; Verghese et al., 2003). Therefore, these studies point indirectly to neuronal adaptations resulting from being active during leisure time. To our best knowledge, our study is the first demonstrating robust neural effects induced by a true leisure activity, meaning that individuals of our training group had different training schedules and strategies depending on a variety of external factors, such as the time available for leisure activities or the teaching style of their individual golf instructor. Thus, the present study expands our knowledge about training-induced neuroplasticity by demonstrating effects of a motor training that has an improved ecological validity.

The process of learning to play golf comprises adaptations in motor functions, visuospatial functions and body perception/control. These functions correspond well to regions showing training-related gray matter changes. Firstly, the ventral premotor cortex has been repeatedly associated with mental imagination and movement observation (Binkofski & Buccino, 2006; Caspers et al., 2010), both of which represent important strategies of motor skill learning, especially in early stages of the learning process. Movement observation, in turn, is closely related to movement imitation with both relying on the mirror neuron circuit including the inferior frontal gyrus, the ventral premotor cortex, and the inferior parietal cortex (Buccino et al., 2004). Concerning the observed adapta-

tion in the vicinity of the dorsal and ventral premotor cortex, the primary somatosensory cortex and the inferior frontal gyrus, the generative assembly device (GAD) may be regarded as an alternative explanation (Corballis, 1991). The GAD proposed by Corballis suggests that the above-mentioned areas may be involved in the transformation of single elementary movements into a complex movement representation. In particular, at an early stage of learning the incorporation of single movements in order to execute a complete golf swing is of great importance. Although, the GAD bases mainly on language processes a great amount of work has substantiated that this device includes amongst language processes also the motor system (Baumgaertner, Buccino, Lange, McNamara, & Binkofski, 2007; Rizzolatti & Fabbri-Destro, 2010).

Both lines of research, concerning motor learning and mirror neurons, have emphasized the functional connection between frontal regions (i.e., ventral premotor cortex, inferior frontal gyrus) and the parietal lobe, which is based on extensive anatomical connections (Rushworth, Behrens, & Johansen-Berg, 2006). Accordingly, we found training-induced changes in rostral and caudal parts of the inferior parietal lobe (IPL). The supramarginal gyrus, which is part of the rostral inferior parietal lobe, has been suggested to be important in planning goal-oriented actions (Tunik et al., 2008), particularly with respect to the integration of multimodal information (Eickhoff et al., 2010). Proprioceptive and tactile but also visual information needs to be precisely integrated prior to the execution of a broad but accurate arm movement. Consistent with this idea, the rostral part of the IPL was also shown to be involved in perceiving one's own body (i.e., body ownership) (Blanke, 2005; Tsakiris, Longo, & Haggard, 2010). In contrast, the caudal part of the IPL and the POJ are functionally and anatomically connected to the visual system (Colby & Goldberg, 1999; Culham et al., 2006). The increased gray matter density in the caudal part of the inferior parietal cortex is in good agreement with previous studies investigating structural changes induced by a complex motor training (i.e. juggling) (Draganski et al., 2004; Scholz et al., 2009). Juggling and golf share a variety of similar demands, especially a precise transformation from visual stimuli into a motor command and coding of spatial information.

Interestingly, in the present study we demonstrate a strong positive relationship between the increase in gray matter and training intensity in the right POJ, a critical structure of the dorsal stream. Moreover, participants who practiced with a higher intensity (needed fewer days to complete the 40 training hours) and showed greater structural adaptation in the POJ were those achieving the license to play on the golf course within the 40 practice hours. Although, we are aware that a strict assignment of a given function to a certain structure would undervalue the great complexity and connectivity of the human brain, previous research (i.e, animal studies, lesion studies, neuroimaging studies) provides convincing evidence that the POJ is closely associated with visuo-motor processes, particularly, in the online-control and online-correction of visual guided arm movements (Himmelbach, Karnath, Perenin, Franz, & Stockmeier, 2006; Kravitz, Saleem, Baker, & Mishkin, 2011). In general, our findings suggest that low- and high-intensity trainings are accompanied by a change of neuroanatomical parameters. Beyond that, we pro-

vide evidence that in certain regions differences between subjects practicing with low- or high-intensity can be observed. However, due to two reasons this latter finding must be interpreted with caution. First, in our relatively small sample, subjects practicing with high intensity were also those showing a better performance (in terms of achieving the license to play on golf courses). Thus, the extent of gray matter change may also be directly linked with a certain level of proficiency or with the increase of proficiency. In this case, the relationship is likely moderated by factors (e.g., motivation, or prior experience in other motor skills) favoring a faster skill acquisition within the same amount of training hours. Future studies are needed in order to shed more light on this issue. Second, we demonstrated only for the POJ a strong relationship between structure and behavior. The lack of correlations between training intensity and increases in gray matter in regions other than the POJ may be due to the number of subjects in the golf group, which certainly is at the lower limit for revealing brain-behavior correlations. Thus, we cannot rule out that the statistical power was too low to detect such correlations for further cortical/subcortical regions. Alternatively, it may be that the increase of gray matter volume in regions other than POJ is independent of training intensity, but instead depends on the total amount of training hours between pre- and post-measurements which was the same for all subjects.

Generally, however, it can be concluded that changes in gray matter are closely related to skill level, which in turn depends in large part on training characteristics. Thus, subjects who practiced with higher intensity and reached the license to play on golf courses within the studied training interval are assumed to quickly run through the successive handicap levels in future (provided that training intensity does not decline) – a process that is likely accompanied by a further increase of gray matter. Comparing them to subjects who practiced with lower intensity and who are assumed to run through the handicap levels much slower, one would expect between-group differences in gray matter at a given point in time, which would resemble previous findings of our group showing cross-sectional differences between highly trained and amateur golfers (Jäncke et al., 2009). The present study extends findings of our previous study by showing that structural adaptations due to golf practice can already be observed as early as after the onset of golf training when using a longitudinal approach, which has a higher statistical power.

The results described above are intriguing because they demonstrate that a physical leisure activity practiced with an individual training protocol revealed very similar effects as a more experimentally controlled training. Thus, we assume that a strict and controlled training protocol is not mandatory for training-induced adaptations of gray matter. Beyond this, our findings indicate an interesting relationship between training intensity and the extent of training-induced gray matter change. However, future research needs to clarify whether this relationship is exclusively due to training characteristics or for example due to the higher level of proficiency that accompanies – in case of our subjects – a higher training intensity. Lastly, regarding the practical implications of our findings, we propose that leisure activities performed with low to moderate in-

tensity evoke anatomical changes similar to those evoked by highly controlled trainings in an experimental setting. Thus, leisure activities may be considered as an additional therapeutic setting in the process of neuro-rehabilitation.

5.2 The effect of leisure activity golf practice on motor imagery: an fMRI study in middle adulthood

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Authors contribution:
LB, SM and LJ designed research; LB and SM performed research; LB and SM analyzed data; LB, SM and LJ wrote the paper.

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5.2.1 Abstract

Much is known about practice-induced plasticity of the motor system. But it is not clear how a physical training influences the mental rehearsal of the practiced task and its associated hemodynamic responses.
In the present longitudinal study with two measurement time-points, we used the method of functional magnetic resonance imaging (fMRI) and a motor imagery task, in order to explore the dynamic neuro-functional changes induced by a highly complex physical training. The eleven golf novices between the age of 40 and 60 years practiced the motor training as leisure activity. Additionally, data from an age and sex-matched control group without golf training was collected.
As a main result, we demonstrate that changes between the two measurement time-points were only found in the golf novice group. The golf novices showed a decrease in hemodynamic responses during the mental rehearsal of the golf swing in non-primary motor areas after the 40 hours of golf practice. Thus, the results indicate that a complex physical leisure activity induces functional neuroplasticity in the seldom studied population of middle-aged adults, and that this effect is evident during mental rehearsal of the practiced task. This finding supports the idea that (a) a skill improvement is associated with a modified activation pattern in the associated neuronal network that can be identified during mental rehearsal of the practiced task, and that (b) a strict training protocol is not necessary to induce functional neuroplasticity.

5.2.2 Introduction

The brain shows an enormous capacity to adapt rapidly and efficiently to new requirements and experiences during the process of learning. This capacity is reflected in structural adaptations (Draganski & May, 2008). Closely related with these neuroanatomical changes are the similarly important changes in neural recruitment patterns (Jäncke, 2009; Pascual-Leone et al., 2005). Structural and functional neuroplasticity may be regarded as two processes with a mutual interaction. Meaning, that morphologic changes are accompanied by functional changes and vice-versa (Ilg et al., 2008; Granert et al., 2011). With respect to the different methodological approaches to study neuroplasticity, however, there is a practical differentiation based on the spatial and temporal methodological characteristics. Recent studies from the field of motor skill learning indicate that training-induced structural and functional adaptations occur across the whole lifespan (Lustig et al., 2009; Seidler, 2007). Given the clear focus of these studies on young adults or adults aged over 65, the group of middle aged adults has been neglected, meaning that our knowledge about age-related differences in both the extent and the pattern of training-induced adaptations across the lifespan is still limited.

There is conclusive evidence that the brain relies on the involvement of a widely distributed network including cortical and sub-cortical motor areas, cerebellum and prefrontal areas, independently of age and particularly during the early stages of skill learning (Doyon & Benali, 2005; Halsband & Lange, 2006). As skill improves, the involvement of these neuronal regions changes. Longitudinal studies with a short training duration (i.e., several days) indicate a slowly developing activation increase at early stages of training (Hlustik et al., 2004; Karni et al., 1995; Ungerleider et al., 2002). In contrast, motor experts usually show smaller hemodynamic responses within the sensorimotor system compared with novices performing the same motor task (Jäncke et al., 2000; Koeneke et al., 2004). This effect of expertise is considered to reflect increased efficiency and, hence, reduced neural costs in the neural networks controlling the practiced movements and skills. In addition, less cognitive control (i.e., in terms of reduced attentional demands) is required when a movement is well learned or even automatized (Godde & Voelcker-Rehage, 2010). There is thus far no conclusive study indicating when the transition from increased to decreased neural effort actually occurs.

Most studies on motor learning have registered the neural response to various kinds of finger movements because they are (1) easily performed within the confines of the MR scanner and (2) are not associated with large movement artifacts correlated with the experimental paradigm. To study more complex movements that include several joints and muscles or different body parts such as required for a golf swing, an alternative approach has used the method of motor imagery (Milton et al., 2008). The neuronal networks associated with the imagery of a particular movement from a first-person perspective are strikingly similar to those associated with movements that are overtly executed (Gerardin et al., 2000; Jeannerod, 2001; Lacourse et al., 2005). Several studies have provided strong evidence that training-induced adaptations occur in both types of training protocols, that is, in mentally imagined practice (Olsson, Jonsson, & Nyberg, 2008;

Olsson, Jonsson, Larsson, & Nyberg, 2008; Page, Szaflarski, Eliassen, Pan, & Cramer, 2009) and in physically executed practice (Doyon & Benali, 2005).
In addition to the type of training (overtly performed vs. mental imagery-based), several other training characteristics presumably influence the extent of training-related improvement in performance and associated neural changes. In the motor domain, the preceding longitudinal training studies in healthy subjects strictly applied experimental control in the training situations – keeping training parameters as constant as possible (e.g. training duration per day, overall training duration, training schedule, strategies, etc.). Only few studies have thus far compared different training parameters in terms of their impact on neural plasticity (Studer et al., 2010), while there are no longitudinal studies on the neural effects of a training performed in an environment outside experimental laboratory situations such as during leisure activity. Given that the participation in leisure activities influences the process of brain aging and the risk of developing dementia (Rovio et al., 2005; Verghese et al., 2003), it is important to extend previous research by focusing on training that approximates the real-life situation and has therefore higher ecological validity (Bezzola, Mérillat, Gaser, & Jäncke, 2011).
The present longitudinal functional magnetic resonance imaging (fMRI) study was therefore designed to investigate changes of neuronal recruitment while subjects mentally rehearsed a golf swing that had been overtly practiced between the two fMRI-based measurement time-points. Given the complexity of a golf swing, which requires considerable cognitive and motor control, an extended neural network including cortical, subcortical motor areas, and parietal regions was expected to be associated with mental rehearsal of the golf swing. Our primary interest concerned changes of neuro-functional recruitment patterns in association with golf training, such as activation increases / decreases in the involved brain regions, the recruitment of additional neural resources or the non-engagement of brain regions that were recruited before practice. Several studies (Guillot et al., 2008; Ionta, Ferretti, Merla, Tartaro, & Romani, 2010; Milton et al., 2007; Solodkin et al., 2004) show that the neural activations during mental rehearsal of motor tasks are very similar to the activations identified during physical practice of the same task. Accordingly, expertise effects have been shown to occur during motor imagery (Fourkas, Bonavolontà, Avenanti, & Aglioti, 2008) and motor execution (Jäncke et al., 2000) of the expertise related motor task. These expertise effects were reflected in a more efficient neuronal network, i.e., an increased facilitation of the motor system and a reduced hemodynamic response. Thus, we hypothesized that the neural activations during mental rehearsal of the golf swing will change, in terms of a reduced hemodynamic response, as a consequence of golf practice.

5.2.3 Methods

Participants:
Twenty-two healthy volunteers (18 women, 4 men) with a mean age of 51.2 (SD=7.2) years participated in the present study. A previous study investigating the structural correlates of training-induced plasticity included the same study population (Bezzola et al., 2011). None of the participants had any history of neurological or psychiatric disorder. The study sample consisted of the following two groups, a golf novice group (n=11; 9 women, 2 men) and an age-, sex, and handedness-matched control group (n=11). Handedness was verified by means of the Annett Handedness questionnaire (Annett, 1970). According to this test, 20 participants (10 golf group, 10 control group) were classified as consistent right-handers and 2 participants as consistent left-handers. All subjects gave written informed consent and the local ethics committee approved the present study, in compliance with the Helsinki Declaration.

Experimental design:
A longitudinal study design with two measurement time-points was used. The golf pre-experience of golf group amounted to 77 hours. The interval between the two measurements referred to the golf group and amounted to 40 golf-training hours. Each golf novice had an individual inter-measurement interval, calculated on the basis of the training hours, recorded on a training log. Since each participant of the golf group was matched (age, sex, handedness) to a participant of the control group, we ensured that the two groups had the same inter-measurement interval.

Task:
At both scan time points, participants performed a kinetic motor imagery task. Before each scan session, participants were instructed about the task and advised to perform the imagery task from a first-person perspective, i.e., kinetic motor imagery. We used a block design with three conditions: (1) video condition with a slow motion golf swing (9.7 s) of a professional golf player; (2) motor imagery condition with the mental rehearsal of the own golf swing, i.e., kinetic motor imagery; (3) control condition with a fixation cross lasting as long as the video condition (9.7 s). Each participant watched four epochs of the video sequence. Five imagery conditions followed every video sequence, meaning that each participant performed 20 imagery trials (conditions). The participants were instructed to imagine with their eyes closed their own golf swing from a first person perspective and in slow motion, i.e., approximately 10 seconds. Each participant marked for each trial the beginning and the end of the imagery condition by a button press. The visual presentation and the collection of the behavioral data were controlled with the "Presentation" software (Neurobehavioral Systems, Version 13.0). Before the scanning session and outside the scanner a presentation of the experiment was given, in order to ascertain that the participants understood the instructions. Additionally, after each scanning session questions were asked in order to assess the tactile, spatial and rhythmic difficulties of the imagery task by means of three items (*tactile*, How did the grip feel

while swinging the club?, 1=could not feel my two hands – 7=hands were formed as a unit; *spatial*, How did the position of the club's face feel?; 1=could not feel the club's face – 6=could feel the club's face during swing and its position after impact; *rhythm*, How was the rhythm of the club's face?; 1=could not imagine rhythm – 7=could feel the backswing, the top swing, the acceleration in the down swing, and the follow through).

Data acquisition:

The MRI data were acquired on a 3T Philips Intera whole-body magnetic resonance tomograph equipped with an eight-channel Philips SENSE head coil. Whole brain anatomical images were obtained from 160 slices by using a T1-weigthed three-dimensional gradient echo pulse sequence (turbo field echo TFE). The following acquisition parameters were used: repetition time TR = 8 ms, echo time TE = 3.7 ms, flip angle = 8°, field of view FOV = 240 x 240, slices = 160, spatial resolution = 0.94 x 0.94 x 1 mm3. None of subjects had to be excluded from the study due to anatomical anomalies. Functional data were obtained from 34 slices with a T2*-weighted gradient echo-planar imaging (EPI) sequence, which is sensitive to blood oxygenation level-dependent (BOLD) contrasts. The following acquisition parameters were used: TR = 2100 ms, TE = 35 ms, flip angle = 77°, FOV = 220 x 136 x 220, acquisition matrix = 80 x 80, voxel size = 2.75mm x 2.75mm x 4.0mm, slice thickness 4.0mm, sensitivity encoded (SENSE).

Behavioral data analysis:

The statistical analysis of the imagery duration was performed with a repeated-measures ANOVA (within-subject factor "time" and between-subject factor "group"). The items, concerning the imagery capability, were statistically analyzed using the Kruskal-Wallis test.

fMRI data analysis:

Artifact minimization and fMRI data analysis was performed with the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2010a (Mathworks Inc., MA, USA). The following preprocessing steps were performed: (1) realignment to the first volume in order to correct for movement artifacts, (2) normalization to the standard stereotactic space (EPI template provided by the Montreal Neurological Institute), (3) smoothing with a Gaussian kernel of 8mm full-width-at-half-maximum. Activated voxels were identified by the general linear model approach, implemented in SPM8. At first-level analysis, for each participant a model with two sessions (T1, T2), three condition regressors (video, imagery, button press movement) and six movement regressors (with the realignment parameters) was aligned. The video regressor was modeled as an epoch lasting 9.7 s with the onsets of the video sequence. The duration of the imagery epoch was defined by the difference of the two key presses, indicating the start- and endpoint of the imagery phase. In order to disentangle the purely motor activity of the motor response induced by the key press, an additional regressor was included in the model. This regressor (i.e. response) bases on the onsets of the second key-press (indicating the

end of the imagery phase) and was modeled as an event. A high-pass filter with a cut-off of 128 seconds was applied to eliminate slow signal drifts. We were particularly interested in the following contrasts: motor imagery vs. response (motor imagery contrast; subsequently abbreviated with MI) and video vs. baseline (video contrast; subsequently abbreviated with V). To permit population-level inferences random effect analyses were applied. Thereby, maps of contrast coefficients for each of the first level contrasts were collectively submitted to three analyses of variance (ANOVAs). Two one-way ANOVAs with the between-subject factor group (golf group, control group) were performed - for the video contrast V at time-point 1 and for the motor imagery contrast MI at time-point 1. In order to investigate the training-induced changes of functional recruitment during motor imagery MI, a repeated-measures ANOVA (i.e., flexible factorial model in SPM8) with within-subject factor time (T1, T2) and between-subject factor group (golf group, control group) was performed. The t-maps resulting from the two one-way ANOVAs were analyzed at a cluster threshold of $p<.001$ and FWE (Family-Wise-Error)-corrected at cluster level. Clusters from the repeated-measures ANOVA were reported if they survived the significance threshold of $p<.001$ (uncorrected) with a spatial extent of k=30 voxels. The cluster locations were labeled using the Julich Histological atlas. In order to ascertain that changes in the hemodynamic response seen in the golf group can exclusively be ascribed to the golf training, we performed an additional interaction analysis. This analysis bases on regions-of-interest (ROIs) extracted from the clusters showing a significant change between the two measurement time-points in the golf group. Accordingly, we created ROIs by using the marsbar tool (http://marsbar.sourceforge.net/) and the center coordinates were defined by the local maxima of the repeated measures ANOVA (i.e., significant changes between the two measurement time-points in the golf group). We calculated for each ROI and for each subject the mean beta-estimates during the motor imagery condition (i.e., MI contrast images). The extracted values were further analyzed using SPSS19 (http://www.spss.com). A repeated-measures ANOVA was calculated with the within-subject factor “time” and the between-subject factor “group”.

5.2.4 Results

Behavioral data

Variations in the overall imagery duration were investigated by means of a repeated-measures ANOVA with the within-subject factor "time" and the between-subject factor "group". This analysis neither showed a significant interaction effect nor a significant main effect. Furthermore, after each scanning session participants rated the difficulty to imagine a golf swing by means of three items. At both time-points and for each item, the ratings did not differ significantly between the two groups (Table 5.2).

Table 5.2: *Self report of the imagery competence*

	Group	***M***	***SD***
Tactile T1	golf	4.0	2.4
	control	4.2	2.3
Tactile T2	golf	6.0	1.2
	control	5.5	1.1
Tactile T1	golf	4.0	2.4
	control	4.2	2.3
Tactile T2	golf	6.0	1.2
	control	5.5	1.1
Tactile T1	golf	4.0	2.4
	control	4.2	2.3
Tactile T2	golf	6.0	1.2
	control	5.5	1.1

Imagery competence scores for each group at each time-point.

fMRI results: Neuronal activity in the experimental conditions (MI, V) at T1

In a first step, we were interested in the hemodynamic response during the two conditions (MI, V) at T1 for both groups. This analysis bases on the whole brain data. During the imagery condition MI activity was mainly observed in secondary motor areas, sub-cortical regions (nucleus caudatus), as well as the superior parietal cortex (Figure 5.4, Table 5.3). Independent of group, the video condition V was associated with an increased hemodynamic response in vision relevant regions, in particular the bilateral occipital cortex. Along with the occipital cortex, this cluster included also the superior parietal lobule. In addition, the ventral and dorsal PMC (bilateral) showed to be involved while participants watched a slow-motion golf swing movement (Table 5.4).

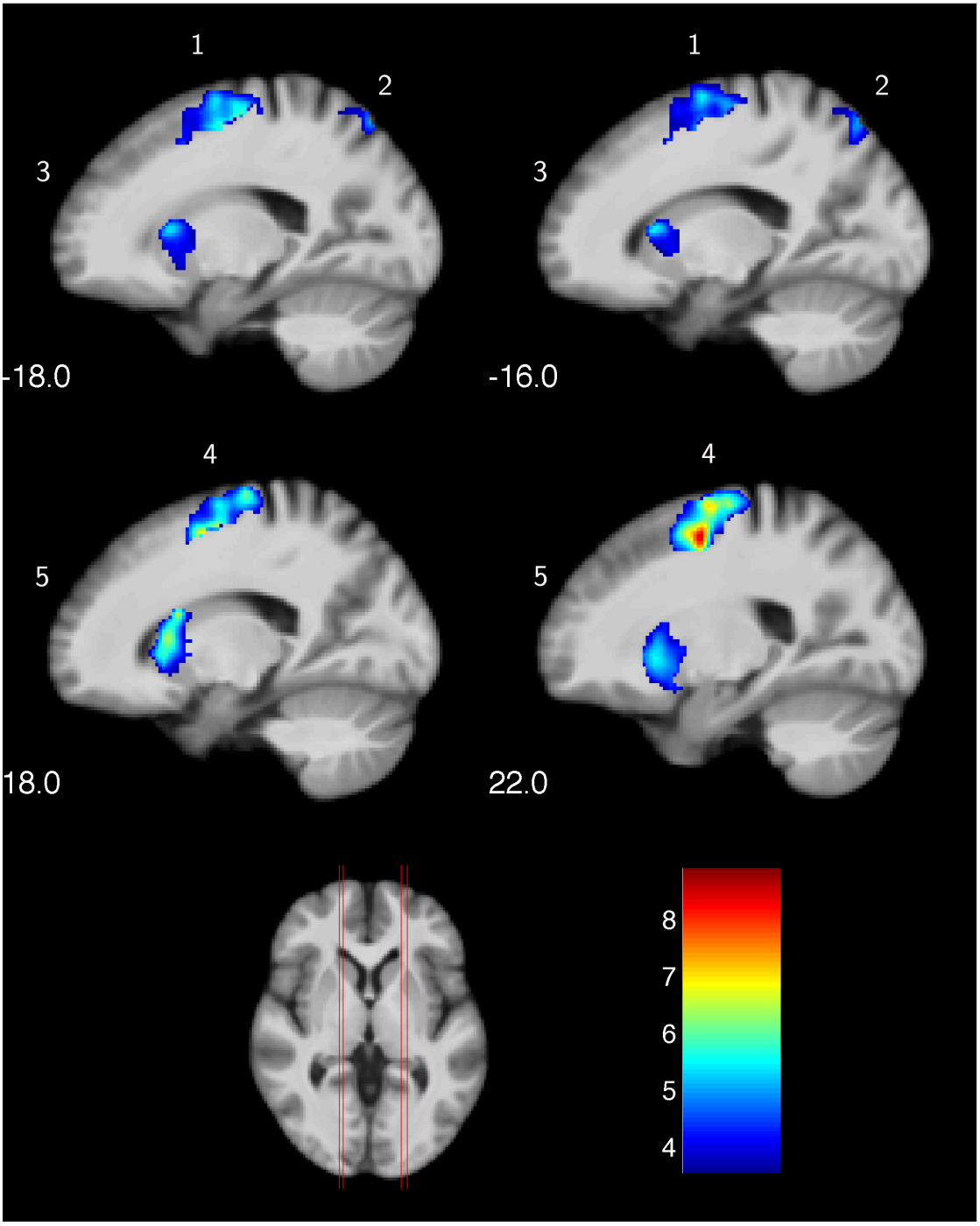

Figure 5.4: Increased hemodynamic response while mentally rehearsing a golf swing (MI) in the golf and control group at baseline (T1). (1) left premotor cortex; (2) left superior parietal lobe; (3) left nucleus caudatus; (4) right premotor cortex; (5) right nucleus caudatus. The color bar represents the T-values.

Table 5.3: Motor imagery contrast (MI) at T1

Anatomical area	**Hem.**	**MNI**			**t**	$\mathbf{k_E}$	***p***
		x	y	z			
dPMC / SMA	R	22	-4	52	8.91	4907	0.001
Nucleus Caudatus	R	18	12	18	6.5	702	0.001
Nucleus Caudatus	L	-16	16	8	5.64	527	0.001
SPL / Precuneus	L	-18	-74	56	5.25	479	0.001

Motor imagery contrast (MI; golf and control group) at T1 with activation peaks, hemisphere (Hem.), their local maxima coordinates (MNI), T-values, size of respective cluster (k_E), and significance level. dPMC = dorsal premotor cortex; SMA = supplementary motor area; SPL = superior parietal lobe.

Table 5.4: Video contrast (V) at T1

Anatomical area	**Hem.**	**MNI**			**t**	$\mathbf{k_E}$	***p***
		x	y	z			
Middle Occipital Gyrus	L	-20	-96	-4	16.52	28106	0.001
Hippocampus	R	20	-32	0	8.72	312	0.001
dPMC	L	-28	-4	52	7.56	1272	0.001
vPMC	R	44	0	52	6.73	2016	0.001

Video contrast (V; golf and control group) at T1 with activation peaks, hemisphere, their local maxima coordinates (MNI), T-values, size of respective cluster (k_E), and significance level. dPMC = dorsal premotor cortex; vPMC = ventral premotor cortex.

fMRI results: Training-induced changes in functional recruitment during MI

Significant changes of neuronal recruitment were only observed in the golf group and not in the control group. While mentally rehearsing a golf swing, the golf group demonstrated a significant decrease of neuronal recruitment from the first to the second measurement time-point (i.e., T1 > T2), in the right and left dorsal premotor cortex (Figure 5.5, Table 5.5). The other tests investigating changes between the two time-points, i.e., increases during MI as well as decreases and increases during the video condition, did not differ with respect to neuronal recruitment patterns. Equally as the previous section, these results base on the analysis of whole brain data.

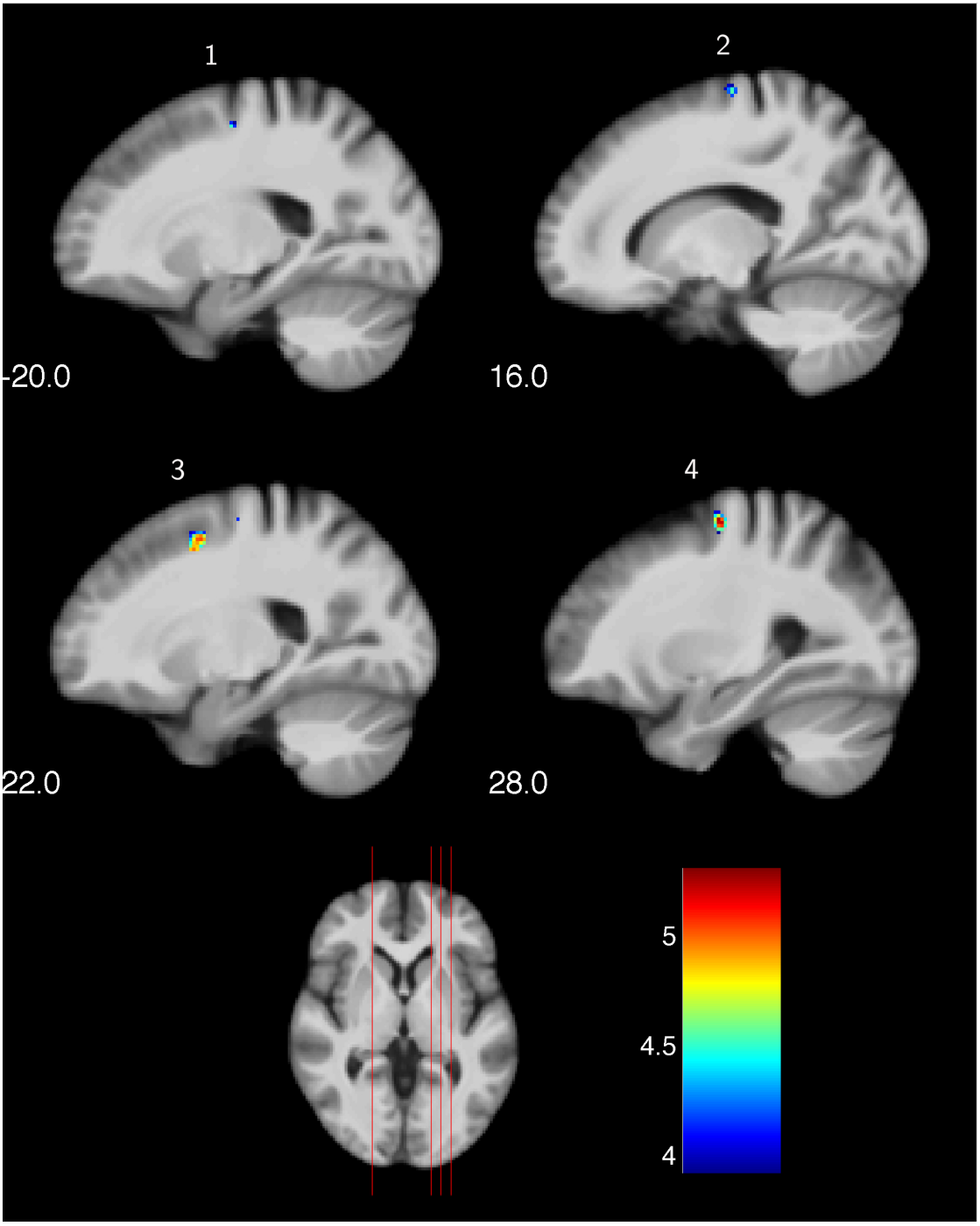

Figure 5.5: Training-induced changes of neuronal recruitment while mentally rehearsing a golf swing (MI). (1), (2), (3) right premotor cortex; (4) left premotor cortex. The color bar represents the T-values. The indices relate to the numbers used in Table 5.5 and Figure 5.6.

Table 5.5: Training-induced decrease (T>T2) of functional recruitment during MI

Anatomical area	**Hem.**	**MNI**			**t**	$\mathbf{k_E}$	***p***
		x	y	z			
dPMC	R	28	-14	58	5.31	58	0.001
dPMC	R	22	2	-52	5.28	94	0.001
dPMC	R	16	-18	70	4.69	34	0.001
dPMC	L	-20	-12	54	4.49	33	0.001

Decreases of hemodynamic responses in the golf group with activation peaks, hemisphere, their local maxima coordinates (MNI), T-values, size of respective cluster (k_E), and significance level. dPMC = dorsal premotor cortex. The indices relate to the numbers used in Figure 5.5 and Figure 5.6.

Interaction analysis "group x time-point"

The changed hemodynamic response in the golf group during MI was further confirmed by the interaction analysis (Figure 5.6) with the ROI-approach. In the right and left PMC the golf group demonstrated significant decreases of activation, while significant changes in the control group were absent.

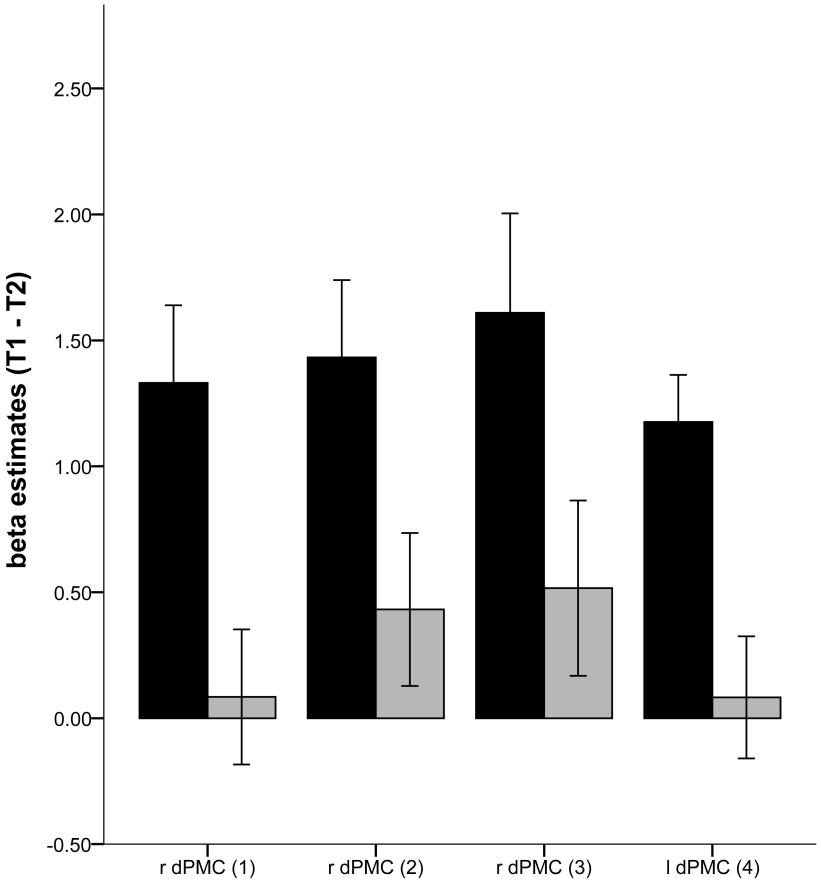

Figure 5.6: Interaction effects for changes of neuronal recruitment during MI, between the golf (black) and the control (gray) group: dPMC = dorsal premotor cortex. The indices relate to the numbers used in Table 5.5 and Figure 5.5. Error bars represent 1 SE.

5.2.5 Discussion

The present longitudinal study sought to delineate the effects of golf training on neural recruitment patterns associated with mentally rehearsing a golf swing. As hypothesized, we observed reduced hemodynamic responses during motor imagery of the golf swing at post- compared with pre-training measurements. These changes in neural recruitment were seen in task-relevant cortical regions and were limited to the golf group. In the following, we first discuss the general pattern of activation seen in both groups at pre-training measurements and then address the issue of training-induced changes.

Neural underpinnings of mentally rehearsing a golf swing

While mentally rehearsing a golf swing, subjects of both groups (having no or very little previous golfing experience) demonstrated neural activity in a large network including cortical and sub-cortical sensorimotor regions and in areas of the dorsal stream. This finding agrees nicely with previous research on the neuronal underpinnings of motor imagery (Jäncke, Kleinschmidt, Mirzazade, Shah, & Freund, 2001; Lotze & Halsband, 2006). These demonstrated that secondary cortical motor areas (e.g., premotor cortex and supplementary motor area) and the parietal lobe were strongly involved in the preparation of mental movements that were not executed overtly. Especially novices or subjects with a low skill level have been shown to recruit a large neural circuit while mentally rehearsing the untrained movement (Milton et al., 2007; Olsson, Jonsson, Larsson, & Nyberg, 2008; Ross et al., 2003). Consistent with the activation of the basal ganglia, several of these subcortical nuclei have been repeatedly shown to play a critical role during the process of skill learning, especially when a new motor sequence has to be learned (Doyon et al., 2009).

Training-induced changes

The results of the repeated-measure ANOVA for comparing pre- and post-training activation patterns indicate changes of task-related brain activation in the golf group, while this effect was not observed in the control group. Specifically, we found a reduction of task-related brain activation from pre- to post-training predominately in the right dorsal premotor cortex.

Our finding of reduced activation at post-training measurement is well in line with previous studies on the neuronal underpinnings of motor expertise and motor skill learning. Milton and co-authors (2007), for example, demonstrated that the organization of the involved neuronal network during the pre-shot routine of a golf swing differs depending on the level of expertise. Compared with golf novices, golf professionals recruited a smaller and more focused neuronal network during the preparatory phase that precedes the golf swing. Further evidence that the training effect is reflected in a decrease of brain activation while performing expertise-similar movements is provided by cross-sectional studies with highly trained experts in other domains, such as musicianship (Jäncke et al., 2000; Koeneke et al., 2004). But previous studies also suggest that the phenomenon of training-induced reductions in neural activity is not exclusively tied to the extreme

amount of practice seen in professional athletes or musicians. There is little evidence from longitudinal neuroimaging studies in novices that a reduction of the hemodynamic response might occur already at early stages of learning, that is, after a few weeks of real or mental practice (Hlustik et al., 2004; Koeneke, Lutz, Esslen, & Jäncke, 2006; Ma et al., 2010). However, the pertinent literature does not allow clear conclusions regarding the time point of transition from the initial phase of activation increase (Hlustik et al., 2004; Karni et al., 1995) to the phase where activation drops below the pre-training level.

We suggest that the observed decrease of neuronal activation is explained by a training-induced increase in neuronal efficacy. Based on the preceding findings, it was hypothesized that individuals execute or prepare a well-trained (as a consequence of practice) motor task more efficiently, with less effort, and with less degrees of freedom (Bernstein, 1967; Jäncke et al., 2000). The latter point refers to the theoretical view that a higher skill level is accompanied by more integrative motor control. Through experience this control process makes use of synergies by linking different effectors (e.g., number of limbs, joints, etc.) together functionally - meaning that more effectors may be supervised simultaneously without the need for separate control of each effector (Tuller et al., 1982). Concerning the decrease of neuronal activity in the premotor cortex, we assume that golf training influences motor control processes of the golf swing by reducing the number of degrees of freedom. Accordingly, the golf group might require less neural effort to mentally control the golf swing at post-training measurement. We further hypothesize that skill improvement and the associated increase in motor control efficiency impacts on both types of movement – the execution of the real golf swing and the mental rehearsal of the golf swing. Increased competence in imagery at post-measurement may provide an alternative explanation for reduced hemodynamic response at post-measurement. This assumption is based on work showing that participants with better imagery performance do so in association with a less extended recruitment pattern (Guillot et al., 2008). The fact that the golf novices did not rate the imagery competence differently between the two measurement time-points argues for a minor role of this factor in the present study. But our self-report measure of imagery competence is of course only a rough indicator that might not entirely reflect true behavior (this being a common drawback of imagery studies). Given that these two explanations are not mutually exclusive, a combination of both explanations might be relevant for the present findings.

In the present study, a decrease of neuronal recruitment was primarily located in the right hemisphere. Learning-related dynamic processes in the two hemispheres might be considered a possible explanation of this lateralization effect. Motor learning is known to induce a decrease of activation in areas belonging to the right hemisphere, whereas areas belonging to the left hemisphere rather show an increase of neuronal involvement (Serrien et al., 2006). In accordance with this dynamic view of hemispheric particularities, the study by Debaere and co-authors (2004) demonstrated learning-related activation decreases in right-hemispheric regions, including the right premotor cortex, over a four-day course of complex hand training (Debaere et al., 2004). In contrast, areas

belonging to the left hemisphere showed a more prominent role at later stages of the learning process. The authors suggested that changes in task complexity or attention might induce a take-over from the right to left hemisphere. But given the highly complex imagery task and the unusual environment (i.e., scanner noise and supine body position), we doubt that the reduced involvement of the right premotor cortex can be explained by less attentional demands in the present study. Instead, changes in task complexity may be related to the suggestion of a more efficient network and thus explain the present functional plastic adaptations in the golf group. Clearly, future research is needed to disentangle these factors (e.g., attentional demands, task complexity, imagery competence) that potentially influence this training-induced improved neuronal network.

In contrast to the previous studies (mentioned above) based on very simple motor tasks such as finger tapping or finger sequence learning, the present golf motor training consisted of complex movements. Learning to play golf puts high demands on motor and cognitive control processes that are necessary to prepare the golf swing, accomplish the eye-body coordination, and control movements of different body parts with exact timing. Importantly, training was performed as a true leisure activity with highly individual training protocols and parameters. In contrast, previous studies have attached great importance to keeping training parameters constant across subjects in order to optimize effect strengths (Lustig et al., 2009). To the best of our knowledge, our mental rehearsal study is the first to demonstrate the induction of robust effects at the level of neural activity by a true leisure activity. Thus, the present study expands our knowledge about training-induced neuroplasticity by demonstrating effects of a motor training that has an improved ecological validity.

A further new aspect of the present study relates to the age of the studied cohort. To date, use of motor imagery to examine the neural mechanisms of motor learning has focused primarily on young study populations. However, behavioral studies show substantial age differences during the process of motor learning, specifically in terms of age-distinct learning curves (Verwey, 2010; Verwey et al., 2011). So far, the question of age differences in the neuronal representation of motor imagery has not been addressed. Although the present study with its relatively small group size has not the appropriate design to answer this question, the present findings do indicate that participants in their middle adulthood show comparable neuronal recruitment patterns as younger participants in previous studies (Szameitat, Shen, & Sterr, 2007). Furthermore, the present results demonstrate that training-induced functional plasticity is not a process limited to young adults, thus providing further evidence that brain adaptations due to skill learning can occur across the whole life span – also in middle adulthood. Future intervention studies with different age groups (young adults, middle aged adults, old adults) or studies including a larger sample size are needed in order to shed more light on this issue.

Conclusion

Taken together, our results extend previous research in various aspects. Our findings in-

dicate that 40 hours of training of a complex physical leisure activity induces functional neuroplasticity. This process is reflected in a pre-post training reduction in neuronal activity in task-relevant cortical areas during the mental rehearsal of a golf swing. Furthermore, this applies for the population of middle-aged adults that has as yet received scare attention in research. These findings support the idea that improved skill is associated with greater efficiency in associated neuronal networks. The training-induced improvement in skill appears to influence the neural processes associated with imagery of practiced movements. Finally, our findings suggest that motor training protocols characterized by a low-to-moderate training intensity and a highly individual training schedule, and therefore by high ecological validity, are effective in inducing functional neuroplastic changes.

6 General discussion

By following the rarely taken path of longitudinal study designs, the present dissertation aimed to investigate training-induced changes of brain anatomy and brain function. Data derived from a longitudinal design are needed in order to describe the full individual potential of structural and functional adaptations of the nervous system in the context of complex motor learning, in particular during an early stage of learning. The examined intervention of the present dissertation consisted of a golf training performed by golf novices as a leisure activity. The selection of this type of intervention was motivated by the following three factors: (a) learning to play golf is a physical activity not restricted to a certain age group, (b) it consists of a complex motor learning task with high cognitive and motor demands, and (c) it can be practiced as a leisure activity. The latter point alludes that learning to play golf can be performed alongside occupational commitments of the age group we studied. In order to investigate anatomical changes induced by the golf training we applied the method of voxel-based morphometry in the first study. The second study used the fMRI method to shed more light on the underlying functional mechanisms of the golf training.

6.1 Training-induced neuroplasticity and associated morphologic changes

The research line of structural neuroplasticity has indicated that motor trainings induce anatomical changes in terms of a changed macroscopic architecture of gray and white matter, already at an early stage of training (Taubert et al., 2010; Driemeyer et al., 2008). Based on this former research, we hypothesized that the golf novice group would demonstrate training-induced adaptations in gray matter in brain regions demanded by the golf training (first working hypothesis; see chapter 3.4).
Two main findings of the first study provide support for this hypothesis. First, 40 hours of golf training showed to induce an increase in gray matter in task-relevant cortical regions encompassing sensorimotor regions and areas belonging to the dorsal stream. More precisely, the increases of gray matter were observed in the following regions: ventral part of the left central sulcus, left ventral premotor cortex, left rostral inferior parietal lobule, left intraparietal sulcus, right parieto-occipital junction, and the caudal part of the right inferior parietal lobule. This finding is in good agreement with previous longitudinal studies demonstrating fast macroscopic changes of gray and white matter induced by a motor training (Taubert et al., 2010; Driemeyer et al., 2008). Functions that are assumably affected by the golf training, such as motor functions, body perception and control, and visuospatial functions, correspond well to the cortical regions that show

training-related morphologic changes (Blanke, 2005; Buccino et al., 2004; Halsband & Lange, 2006; Kravitz et al., 2011). Second, structural adaptations in the right parieto-occipital junction (POJ) were strongly related to the intensity of training. Participants, who needed less time to achieve 40 training hours were those who showed greater gray matter increases in the POJ. As a critical structure of the dorsal stream, the POJ is closely associated with visuomotor processes, particularly with the on-line control and correction of visually guided arm movements (Himmelbach et al., 2006; Kravitz et al., 2011). However, this correlation of training-intensity and the percent increase of gray matter in the POJ has to be interpreted with caution. The reason for this cautious conclusion relies on the fact that the participants showing the largest increases of gray matter in the POJ were (a) those who achieved the license to play on the golf course during the study period and (b) those with a more intense practice routine, i.e., achieving the 40 training hours in a shorter time period. Thus, the extent of gray matter change may also be directly linked with a certain level of proficiency or with the increase of proficiency. In this case, an alternative variable, such as motivation or prior experience in other motor skills, may favor a faster skill acquisition within the same amount of training hours.

Taken together, the present study indicates that a physical leisure activity induces training dependent changes in gray matter - already at an early stage of the learning process. Furthermore, the practice-induced gray matter changes were localized in the expected neural network, namely regions of the dorsal stream and regions belonging to the sensorimotor system. Hence, the first and the fourth research questions can be affirmed and are supported by the findings of the present study, which investigates structural neuroplasticity by means of a longitudinal study design.

6.2 Training-induced neuroplasticity and associated functional changes

Previous research has shown that in addition to structural adaptations, motor trainings also induce functional neuroplasticity. Consequently, with the second study we sought to delineate functional changes of neuronal recruitment accompanying the golf training. For obvious reasons, mainly related to the MR environment, a mental imagery paradigm was applied where subject had to mentally rehearse a golf swing. Since participants of both groups had no (i.e., control group) or very little golf experience (i.e., golf novice group) - meaning that they were not advanced players - we hypothesized an extended neuronal network to be involved during the process of mental motor imagery. More importantly, we hypothesized that the intervention of the physical golf training in the golf group would be reflected in functional changes between the two measurement time points. In contrast, no changes of functional recruitment were expected in the control group.

The findings of the second study provide support for these two hypotheses. First, we demonstrated that both groups recruited a spatially extended neuronal network while

mentally rehearsing a golf swing. The general activation pattern at pre-measurement included cortical and sub-cortical sensorimotor regions as well as areas belonging to the dorsal stream. There is strong evidence that novices or subjects with a low skill level involve a large neural circuit while mentally rehearsing an untrained movement (Ross et al., 2003; Milton et al., 2007; Olsson, Jonsson, Larsson, & Nyberg, 2008; Lotze et al., 2003). This novice network contrasts with that of motor experts, which has been demonstrated to be more focused with fewer involved regions. More importantly, we observed reduced hemodynamic responses during motor imagery of the golf swing at post- compared to pre-training measurements. These changes in neural recruitment were seen in a task-relevant cortical region, namely the right premotor cortex. It has to be mentioned that significant changes of neuronal recruitment were limited to the golf group, whereas the control subjects did not reveal changes between the two measurement time points. This finding of reduced activation at post-training measurements corresponds well with previous studies investigating the neuronal underpinnings of motor expertise (Jäncke et al., 2000) and motor skill learning (Koeneke, Lutz, Esslen, & Jäncke, 2006; Hlustik et al., 2004; Ma et al., 2010). Thus, we assume that the observed decrease of neuronal activation is explained by a training-induced increase in neuronal efficacy. A more efficient neuronal network implies that less neuronal effort is needed in order to execute a task. Thus, this increased neuronal efficacy may be reflected in a reduction of brain activity. Furthermore, the decrease of neuronal recruitment in the right premotor cortex at post-measurement is in good agreement with a motor training induced lateralization effect, which has been reported in previous studies (Serrien et al., 2006; Debaere et al., 2004). In these studies, motor learning was shown to be related to a decrease of activation in areas belonging to the right hemisphere, whereas areas belonging to the left hemisphere showed an increase of neuronal activation. Referring to these previous studies, we assume that the reduced involvement of the right premotor cortex can be explained by a reduction in task complexity.

The results of this second study demonstrated that the intervention of the golf training practiced as a *true* leisure activity might induce functional neuroplasticity, which is reflected on a changed neuronal recruitment pattern. Furthermore, irrespective of the investigated group, motor imagery showed to be associated with a large neuronal network including motor-task relevant regions. Consequently, the findings of the second study confirm the second and third working hypotheses (see chapter 3.4).

6.3 Relationship between structural and functional neuroplasticity

The two studies of this dissertation suggest that a leisure activity, with a low-to-moderate training intensity, elicits neuroanatomical as well as neurofunctional changes. Accordingly, the present findings support the idea of the existence of two concurrent processes reflecting training-induced neuroplasticity. These two dynamic processes - the increase of gray matter and the decrease of neuronal activity - are interpreted as a consequence

of an improved skill level. In this context and by taking a more overarching perspective, these two studies allude to the strong relationship between structural and functional neuroplasticity. Independent of the applied method, changes were localized in task-relevant areas, including the sensorimotor system as well as the dorsal stream. In accordance with this overall finding, Ilg and coauthors demonstrated learning-induced (i.e., mirror reading) plasticity by combining structural and functional MRI in a longitudinal study design (Ilg et al., 2008). Data from this study and from the present work, suggest that neurofunctional and neuroanatomical changes occur simultaneously. Similar to the present dissertation study, Ilg and colleagues did not localize the anatomical and functional changes in the exactly same brain regions, except for one region. However, it has to be mentioned that the functional changes strongly depend on the applied fMRI task and for this reason we would not expect an exact match with the location of structural change. This methodological issue does also refer to the present dissertation, since functional neuroplasticity was measured indirectly using an imagery task (i.e., motor imagery of the golf task), which was not practiced. Hence, the present dissertation cannot answer the question on the influential role of structural neuroplasticity onto functional neuroplasticity or vice versa. Future studies are needed in order to shed more light on the mutual interactions of structural and functional plasticity (see 6.6).
A new approach in which the functional correlates relate less on a certain task, namely by means of a fMRI-based resting state approach, might provide new insights for research with the overarching perspective of structural and functional neuroplasticity. Accordingly, by means of longitudinal study, Taubert and co-authors demonstrated recently a close association between training-induced functional connectivity changes (i.e., changes in the resting state network) and macroscopic structural alterations (i.e., gray matter changes and changes in white matter fibre structure) (Taubert, Lohmann, Margulies, Villringer, & Ragert, 2011). However, in order to gain a better understanding on the underlying mechanisms and the interaction between the two types of neuroplasticity further research is needed. A possible direction may be the implementation of multimethod longitudinal approaches, such as the simultaneous recording of EEG and fMRI as well as the measurement of anatomical parameters.

6.4 Leisure activity induced neuroplasticity

A plethora of research has been dedicated to investigate the underlying neuronal and behavioral effects of motor trainings (*for a review see* Draganski & May, 2008; Lustig et al., 2009). One line of research, consisting of longitudinal intervention studies with highly controlled training situations (Draganski et al., 2004; Boyke et al., 2008; Driemeyer et al., 2008), and cross-sectional studies comparing novices and experts (Münte et al., 2002), demonstrated the influential role of motor trainings on anatomical and functional level. Another research line, mainly approaching behavioral research questions, concluded that the participation in physical leisure activities (a) positively influences the process of brain aging (Kramer et al., 2006; Hillman et al., 2008) and (b) goes along with a lower risk to develop dementia (Rovio et al., 2005; Verghese et al., 2003). Considering

this positive association of leisure activity and brain development as well as the training-induced neuronal plasticity, the present work aimed to bridge the two research lines by investigating the neuroanatomical and neurofunctional correlates of motor-trainings that posses a high ecological validity and reflect a real-life situation. Consequently, the intervention of the present work consisted of a highly individually practiced leisure activity, namely a golf training.

The results of the two studies included in this dissertation are intriguing because they demonstrate that a physical leisure activity practiced with an individual training protocol revealed very similar effects as a more experimentally controlled motor training (Draganski & May, 2008). Thus, we assume that a strict and controlled training protocol is not necessary for training-induced neuronal adaptations. Furthermore, both types of neuroplasticity, structural and functional, demonstrated a susceptibility for a motor training of high ecological validity. Along these lines, we assume that a leisure activity might be regarded as a valid intervention type in order to induce structural and functional neuroplasticity.

By identifying that a leisure activity triggers training-induced neuroplasticity, this work may also have some relevant implications outside the basic research field. In respect to the notion that brain aging may already start in middle aged adults, one may speculate that the positive training-induced effects during middle adulthood may counteract or even prevent age-related degradation of the nervous system - in terms of the "use-it-or-lose-it" idiom. However, this idea of leisure activities as a possible prevention approach for age related brain degradation needs to be validated by future research.

Although the present work focussed on a physical intervention with high ecological validity and little experimental control, training characteristics showed to play a specific role in distinct areas. The first study of this dissertation demonstrated an interesting relationship between training intensity and the extent of training-induced gray matter change in the parieto-occipital junction. However, future research needs to clarify whether this relationship is exclusively due to training characteristics or for example due to the higher level of proficiency. In the present thesis skill proficiency was highly correlated with a higher training intensity (see 5.1 and 6.1). This finding illustrates the difficulty to balance experimental control (i.e, the recording of all training characteristics) and ecological validity.

6.5 Limitations

A number of caveats need to be noted regarding the present work. Although the drop-out quote was fairly low, the relatively small sample size was a major limitation in order to provide further conclusions. A low sample size is often linked with a reduced statistical power. This can be illustrated briefly by the findings of the first study, in which only the parieto-occipital junction demonstrated a significant relationship to the training intensity in the golf group. In addition, we revealed a trend for the relationship between training-intensity and percent increase in the ventral premotor cortex. A possible reason for the lack of significant correlations between training intensity and gray matter changes

in regions other than the parieto-occipital junction may be the number of subjects in the golf group. Thus, in the present dissertation the statistical power might be too low in order to detect further brain-behavior correlations, since these correlations rely on a large sample size.

The present dissertation thesis cannot make specific conclusions about the size of effects that would be expected in a younger or older study population, thus, only a relatively vague conclusion regarding the age effects is possible. This issue might be regarded as a further limitation of the present dissertation. We attached great importance to the investigation of a study population, which has often been neglected in neuroscientific research, namely participants in the middle age range. This aim bases primarily on previous research assuming an effect of age on the magnitude of training-induced structural changes (Boyke et al., 2008; Hyde et al., 2009) as well as on functional recruitment patterns (Lustig et al., 2009; Mattay et al., 2002). We have to acknowledge that an intervention study with different age groups (young adults, middle aged adults, old adults) or a study including a larger sample size can likely add new insights to the influence of age onto training-induced neuronal adaptations. Nevertheless, the findings of the present work indicate that training-induced plasticity is not a process limited to young adults and, thus, this work provides further evidence that brain adaptations due to skill learning can occur across the whole life span – also in middle adulthood.

Concerning the second study, some reservation is needed when investigating the functional correlates of a complex motor task by means of a motor imagery task instead of a "real" motor execution task. Although previous research showed an overlap of the involved areas during covert and overt movements, until now many questions remained unanswered. In particular, there is little knowledge about the overlap of imagined or executed complex movements involving several body parts. Additionally, while participants mentally rehearse a movement little experimental control is possible and thus the simultaneous recording of neurofunctional and behavioral data is not feasible. However, by designing a longitudinal design, we sought to partially overcome these limitations. With a longitudinal study design, we focussed mainly on the effect of the intervention (i.e., neuronal changes between the two measurement time points) rather on the task specific neuronal underpinnings and its associated motor imagery related concerns. Furthermore, we revealed at both measurement time-points a similar neuronal activation pattern, and only the dorsal premotor cortex changed in terms of a reduced hemodynamic response in the golf group. This similarity at both measurement time-points let us assume that the existence of serious changes in task execution, such as changes in strategy, may be excluded. Generally, the findings of the second study confirmed the successful accomplishment of these motor imagery task-related obstacles.

6.6 Implications for future work

The present work confirms and extends previous research investigating the neuronal underpinnings of motor training-induced neuroplasticity. However, these findings gave rise to new research questions and questions regarding the practical relevance.

The first study indicated that training intensity might influence the extent of structural changes. However, since the participants with a more intense training routine were those who passed the entrance examination earlier, it remains unclear how the factors training intensity, skill level and structural neuroplasticity are interconnected. It has to be mentioned that in the present study skill level was measured by means of one question, namely the successful passing of the entrance examination. Consequently, a more objective measurement of skill level, such as a system analyzing the exact movement parameters of the golf swing (e.g., SAM PuttLab), would provide an elegant way to investigate the influence of training characteristics and skill level onto neuroplastic processes.

The present dissertation provides major insights how skill learning may induce changes on neuronal level. Besides these effects of physical activity onto brain anatomy and brain function, there is strong evidence that regularly practiced motor trainings have a beneficial effect on cognitive processes (Hillman et al., 2008; Voelcker-Rehage et al., 2010). Given the complexity of learning to play golf, not only demanding motor abilities but also cognitive abilities, a beneficial transfer of the golf training onto cognitive abilities may be possible. Hence, modern statistical analyses, such as structural equation models, may provide a possible approach to investigate the relationship of training-induced morphologic changes and cognitive transfer effects. These models are common in cognitive performance studies especially when investigating the dynamic processes by means of a longitudinal study design (Ghisletta, Bickel, & Lövdén, 2006; Ghisletta & de Ribaupierre, 2005). It has to be mentioned that the application of such models to understand the relation of structural brain changes and cognitive changes has gained little attention until now (Raz et al., 2008). Concerning the present work, it has to be mentioned that in addition to the neurofunctional and neuroanatomical parameters behavioral data of various cognitive functions were also collected. Hence, this gives us the opportunity for follow-up studies that examine transfer effects and take on a multimethod perspective.

Regarding the practical implications of the present findings, leisure activities may be considered as an additional therapeutic setting in the process of neurorehabilitation. We are convinced that motivation plays an extraordinary role during the process of motor learning, not only in the reduction of drop-outs as in the present dissertation. Hence, motivation may be regarded as a booster for neuroplastic processes in research settings as well as during the process of rehabilitation.

6.7 Conclusion

In the present work, neuroanatomical and neurofunctional correlates of a complex motor training have been investigated using structural and functional MRI. As a main result of this longitudinal study including two measurement time points, we demonstrate that a leisure activity induces neuronal adaptations, which are reflected on anatomical as well as on functional level. These adaptations showed to occur in task relevant brain regions. Furthermore, we revealed an interesting relationship of training intensity and

the extent of training-induced gray matter change. Thus, with this work we make a significant contribution to the research field of motor learning induced neuroplasticity, by demonstrating that a strict and controlled training protocol is not necessary to induce training related adaptations. Additionally, by investigating subjects in the middle adulthood, this work supports the idea that the brain remains its strong capacity for neural plasticity throughout the process of aging.

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Publications

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